Volume 7 **Neurology** *Number 8*

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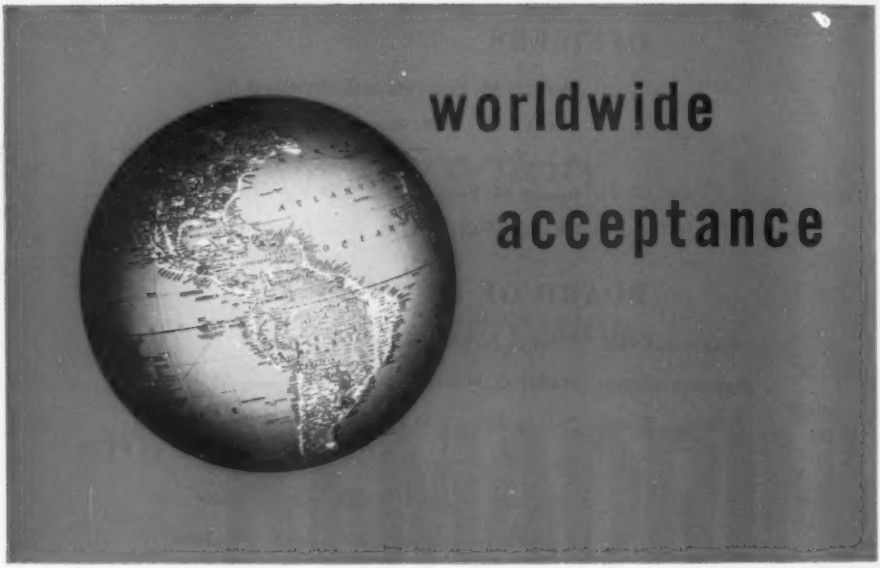

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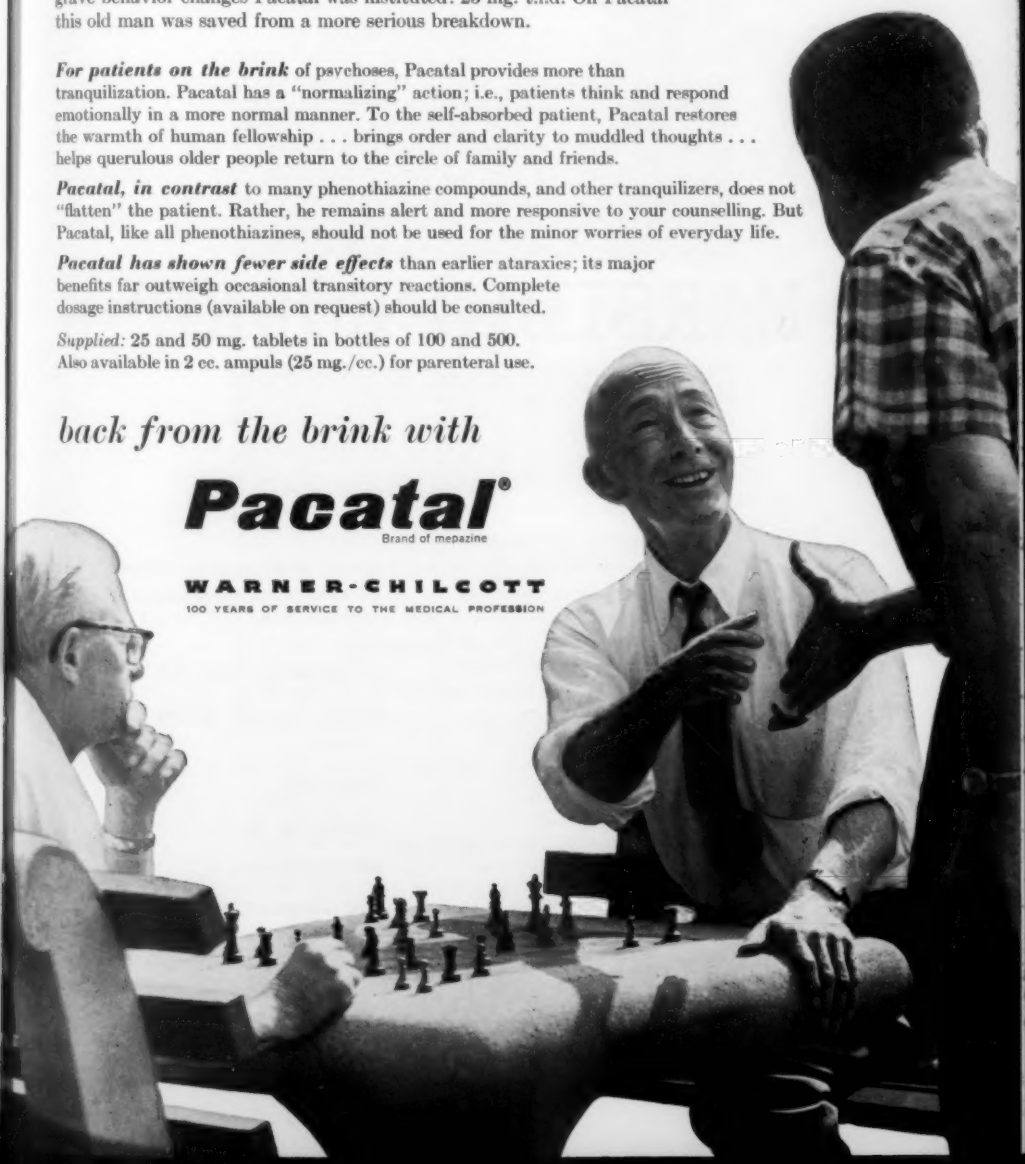

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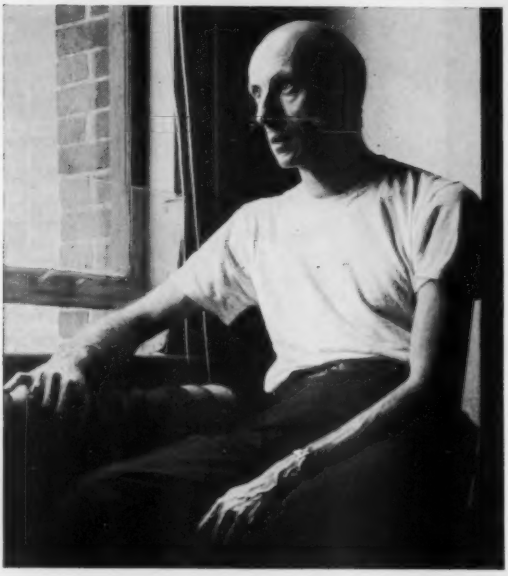

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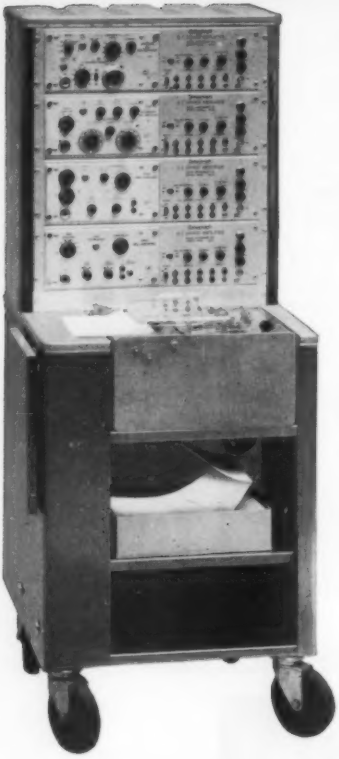

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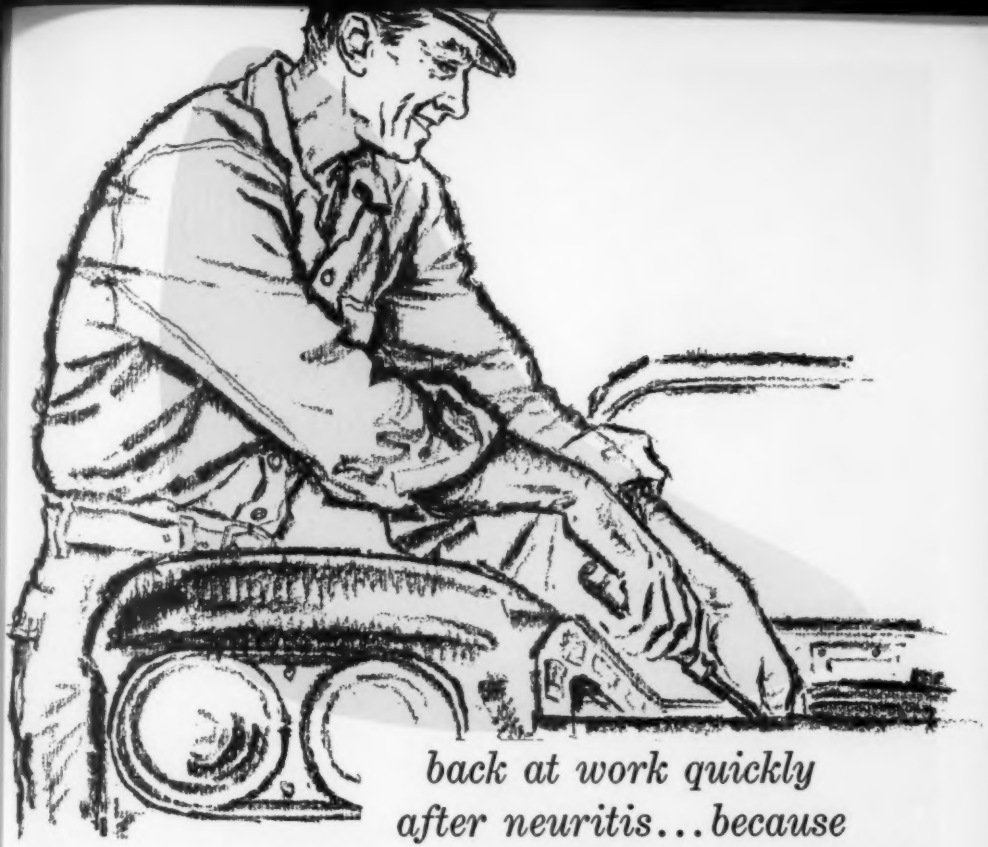

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Syndrome of Acquired Aphasia with Convulsive Disorder in Children

William M. Landau, M.D. and Frank R. Kleffner, Ph.D.

CERTAIN OF THE CHILDREN who are evaluated and taught at the Central Institute for the Deaf are classified as aphasic because they present a specific deficit in the ability to use speech and language.[1] For most of these children the deficit seems to be congenital, since they have failed to acquire the ability to use speech and language normally.[2] Some of them, however, have acquired the ability to use language in an apparently normal fashion and have subsequently lost it. Six such children have been seen in the last two years. One of the six became aphasic and hemiplegic after a severe head injury; the remaining five developed aphasia in relation to a convulsive disorder. These five cases are reported here.

CASE HISTORIES

Case 1. A white male, third of four children, was born in April 1948. Pregnancy and birth history were unremarkable. He was a healthy infant, sat at about six months, and walked before he was a year old. He learned to talk normally at 15 to 18 months. Further behavioral development was also unremarkable. In 1952 when the boy was four, he had one nocturnal generalized seizure. When he was five (July 1953), he developed several furuncles over his face. A few days later he fell in the yard and was found in a semiconscious condition. He staggered into the house and vomited several times. Following treatment with penicillin, it became apparent to the family that the child was having difficulty understanding what was said to him, a defect interpreted as "plain stubbornness." His speech also became garbled.

He was hospitalized in August 1953. His electroencephalogram (figure 1A) showed a generalized spike dysrhythmia, most prominent in the temporal leads bilaterally. Neurologic examination was not remarkable except for the deficit in speech. He was considered to have an aphasic disorder, primarily receptive. Three lumbar punctures revealed two white cells and one red cell per cu. mm.; glucose, 47 mg. per cent; protein, 16 mg. per cent; chloride, 112 mEq. per cent; Lange, negative; Wassermann, negative. The patient was given Dilantin and phenobarbital medication and the seizures were controlled.

When he was first seen at the Central Institute for the Deaf in October 1953, he showed very little use or understanding of speech. His hearing seemed unimpaired. Formal auditory tests were not given since he responded quickly and consistently to a variety of soft sounds. He behaved in a stable and intelligent fashion, although he was clearly frustrated by his difficulties in understanding and using speech. Arrangements were made to have him attend the speech clinic; however, two weeks later the mother called and reported that the child was speaking and understanding normally and that he had been admitted to kindergarten. A repeat electroencephalogram at this time (figure 1B) showed no significant change except that the temporal spikes were somewhat more prominent on the left.

Five months later (March 1954) he had a seizure, with unconsciousness and with clonic jerking in the right hand and arm. In July 1954 he had twitching in his right face, looked pale, and went to sleep. During the rest of the summer he had several episodes of twitching of his right face. He would grab at his right cheek and then sit and rest. On one occasion he said that he was nervous. On other occasions he would take off his right shoe to see if his foot were injured and say, "It feels like my nerves." That fall, during a period of about a week, his comprehension and production of speech diminished rapidly to a level worse than that in 1953. There were no obvious seizures at this time.

In December 1954 he was seen in the pediatric clinic. An electroencephalogram again showed a

From the division of neurology and the Beaumont-May Institute of Neurology, Washington University School of Medicine, and the division of speech pathology and speech correction, Central Institute for the Deaf, St. Louis, Missouri.

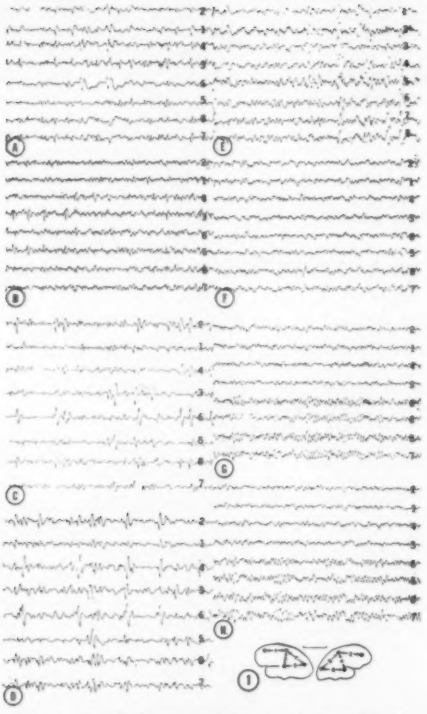

FIG. 1. Serial electroencephalograms in case 1. *A.* August 10, 1953. *B.* October 28, 1953. *C.* December 11, 1953. *D.* January 7, 1955. *E.* March 14, 1956. *F.* April 18, 1956. *G.* May 23, 1956. *H.* August 1, 1956. Descriptions in text.

generalized spike dysrhythmia (figure 1C). Physical examination was essentially unremarkable. Skull films were normal. Roentgenograms of the extremities showed "mild bone retardation." Fasting blood sugar was 74 mg. per cent, nonprotein nitrogen 25 mg. per cent, calcium 12.2 mg. per cent, and phosphorus 4.8 mg. per cent. Hemogram and Kahn test were normal. Urinalysis with examination for porphogens and phenylpyruvic acid was normal. In January 1955 he was hospitalized. Lumbar puncture revealed an opening pressure of 210 mm. of water. There were one polymorphonuclear leukocyte and six lymphocytes per cu. mm. Cerebrospinal fluid protein was 27 mg. per cent, glucose 52 mg. per cent, and Wassermann negative. Psychologic examination indicated that the child was not mentally deficient. His electroencephalogram was unchanged (figure 1D).

Later in January 1955, he was seen again at the Central Institute for the Deaf. His speech was primarily jargon, although occasionally he uttered appropriate words when he was angry or excited. His voice quality and inflection were normal. He could imitate voice pitch and quality changes in the voice with facility, indicating that he had no significant loss of hearing. He was enrolled in the speech clinic but the lessons were discontinued again, this time because of transportation difficulties. His speech did not change during the next year, although there were no seizures. He had increasing difficulty getting along with his siblings and other children.

Neurologic examination in February 1956 showed, in addition to the speech disturbance, some flattening of the lower right face. This was not noted at subsequent examinations. The child was right-handed and right-eyed. His electroencephalogram in March 1956 was unchanged (figure 1E). He was given Paradione, in addition to Dilantin and phenobarbital. An electroencephalogram in April (Figure 1F) showed a mild fast and slow dysrhythmia but without paroxysmal spikes. His mother reported improvement in behavior and some better understanding of speech. The electroencephalogram was even better ordered in May and August (figure 1G and H). Speech continued to improve with special instruction and he was admitted to the first grade of public school on a trial basis in September 1956. He was generally well behaved except when there were changes in his daily routine, such as might be occasioned by visitors or a trip away from home.

The patient's eldest brother (case 2) had a similar disturbance when he was younger. The patient's father had had two nocturnal grand mal seizures following a herniorrhaphy at age 47 and another seizure two years later. The father's electroencephalogram showed a mild degree of fast activity without focalization. Neurologic examination has been normal. The mother aged 41 has had no seizures. Her electroencephalogram showed a mild fast dysrhythmia. Her brother has had some type of blackout spells. An 11 year old brother of the patient had a mild mixed slow and fast dysrhythmia without focalization, but he has shown no clinical symptoms. A 15 month old sister had a normal electroencephalogram. No other relatives have had convulsive or speech disorders.

Summary of Case 1. An eight year old boy with a family history of convulsive disorder developed aphasia on two occasions, once at age five following a series of convulsions, and once without apparent relationship to clinical seizures at age six. Electroencephalograms showed a generalized spike dysrhythmia. In the first episode, speech recovered shortly after anticonvulsant therapy was started. On the second occasion, speech improved with speech therapy as the electroencephalogram improved with increased drug therapy.

Case 2. The first born sibling of case 1 was born in November 1940. Birth, early development, and learning of speech were entirely normal. There were no febrile seizures in infancy. On two

or three occasions at about age eight, usually when he had a sore throat and fever, there were brief episodes of unawareness and eye-rolling. When he was nine years old he fell from his bicycle and bumped the back of his head. Soon after this he was struck on the right side of his head by a swing. On neither occasion was he unconscious or ill. A few weeks after these accidents the parents noticed that he seemed to have trouble with his memory and hearing. He had trouble producing speech, and his mother stated that he could describe some things he couldn't name properly. There was some inconsistency in his response to sounds. The boy, now 15, states that at the time he understood what was said to him but couldn't think of the words he wanted to say.

In August 1950 he was hospitalized and a report at that time stated: "The patient seemed to be attentive to his environment, but would not respond to any spoken command. However, if a loud noise were made to the side or behind the patient, blinking of the lids was noted. There was no tendency to turn his head to the site of the noise. He did not respond to written commands, although he could mimic acts done by the examiner, such as squinting the eyes, protruding the tongue, and so on." Lumbar puncture showed initial pressure of about 100 mm. of water and chemical constituents were normal. Routine laboratory tests including hemogram, urinalysis, and serum calcium, potassium, and sodium were normal. An electroencephalogram showed right hemispheral spike discharges, more prominent in the central leads (figure 2A). Without specific therapy the patient's speech returned in a week or two while he was in the hospital.

The parents neglected to bring the boy back for further examinations until he developed seizures 15 months later. While going to sleep one night he had a frightening dream in which he was being chased. During this time there was a loud buzzing in both ears; he was frightened and ran to his parents' bedroom. There he fell into a generalized convulsion. Two similar attacks occurred in the next few weeks. He was started on Dilantin and phenobarbital medication and since then has had no convulsions. Occasionally he still has a buzzing in his ears about the time he is going to sleep.

In November 1951 (figure 2B) the electroencephalogram showed a mild definite slow dysrhythmia, without focalization or spike discharges. The electroencephalogram was improved in June 1952 (figure 2C). Further improvement was noted in October 1953 and March 1956 (figure 2D and E). Neurologic examination in March 1956 was entirely within normal limits. He was right-handed; eyedness was indeterminate. He was then 15 years old and doing well in the tenth grade.

Summary of Case 2. A 15 year old boy with a family history of convulsive disorder had some minor seizures at age eight. At age nine, following some minor head injuries without serious clinical signs or seizures, he became aphasic for a period of several weeks. At the time there were spike discharges over the right hemisphere in the electroencephalogram. Over a year later he had three generalized seizures, with aura of fear and tinnitus. His clinical condition has remained good without seizures on anticonvulsant medication.

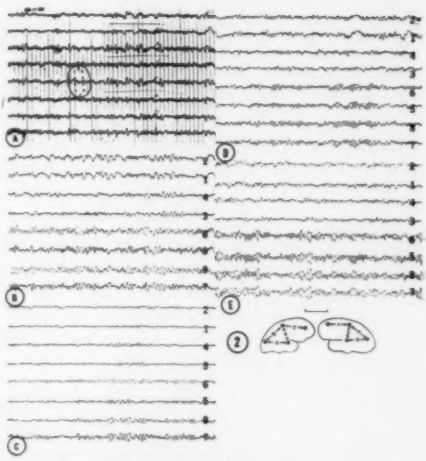

FIG. 2. Serial electroencephalograms in case 2. *A.* August 14, 1950. *B.* November 12, 1951. *C.* June 19, 1951. *D.* October 28, 1953. *E.* March 29, 1956. Monopolar leads as indicated in *A.* Bipolar leads as in diagram in other tracings.

Case 3. A white female, the second of two children, was born in February 1950. There was no family history of convulsive or communication disorder. Pregnancy and labor were uneventful. The baby breathed well at birth and developed normally. She gained weight well and was quite active. She sat at six months, walked at about a year, and was talking between a year and two years. By the age of three she was speaking in full sentences. During the winter of 1953-54 the mother noticed that the child had rather regular involuntary jerkings of her left arm. In May 1954 there was a nocturnal grand mal seizure. Several months later some involuntary jerkings of the left side of the face without loss of consciousness were noted. Five months later there was another nocturnal seizure. In November 1954 the child was seen by a neurologist. Skull roentgenograms and neurologic examination at that time were normal. The electroencephalogram in December (figure 3A) showed a diffuse spike dysrhythmia. Dilantin therapy was begun and no generalized seizures have occurred since then.

By early 1955 (age five) the mother became aware that the patient did not comprehend stories when they were read to her and was only interested in

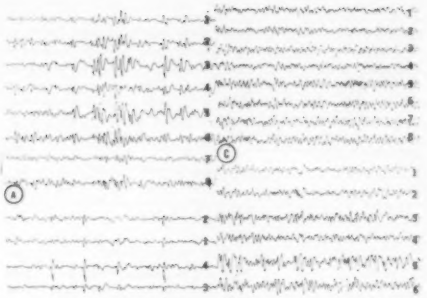

FIG. 3. Serial electroencephalograms in case 3. *A.* November 22, 1954. *B.* March 15, 1956. *C.* May 25, 1956. *D.* September 18, 1956. *E.* December 18, 1956.

the pictures. As her comprehension diminished her speech production became progressively worse until there was practically no speech or understanding when she was first seen at the Central Institute for the Deaf in November 1955. The mother reported that the girl seemed to understand or use an occasional word at home. Formal auditory testing was not done, but her hearing seemed well within the normal range. She imitated silent mouth actions by the examiner and added sound to the actions when the examiner added sound. She turned to a low whistle, to her name, and to voices and noises in the hall outside the examiner's office. The mother reported that when the girl was playing outside she could be called by voice or by whistle. Any attempt to speak resulted in jargon, with normal vocal quality and inflection but without words. She printed several letters on the blackboard spontaneously. The mother reported that about a year previously the girl could print her name and her brother's name correctly. During the examination she could not do this on oral request, but when the examiner printed these names on the blackboard she very readily "copied" them both correctly, though she actually paid little attention to the names printed by the examiner. Psychometric examination at this time using the Advanced Performance Test yielded an IQ of 117.[3] Special speech instructions were begun at this time.

During the neurologic examination in March 1956 the child was alert, friendly, and cooperative. She was right-handed and right-eyed. Although she could imitate movements of the examiner, she could not imitate simple sounds such as "Ah" unless her hand was placed on the examiner's larynx. She could sound consonants and vowels properly from letter symbols in her speech book. The remainder of the examination was normal. Fasting blood sugar was 79 mg. per cent, calcium 10.6 mg. per cent, and phosphorus 4.7 mg. per cent. The electroencephalogram in March 1956 continued to show generalized spike discharges (figure 3B). During a clinical examination ten days later, some twitchings about the left side of the mouth were noted. In addition, there were several spells of blank expression with lip smacking. There was slight flattening of the lower left face at rest. Dilantin medication was increased and phenobarbital was added.

In May the child was much improved. No minor seizures were observed during the interval; she had about 50 useful words. An electroencephalogram showed a moderate degree of slowing but no spike discharges (figure 3C). There was only slight improvement in speech over the summer, and the electroencephalogram showed frequent spike discharges in September (figure 3D). Paradione was started.

By December 1956 her speech had improved further, she could understand some short sentences, and she was more attentive in the teaching process. Behavior was good, there were no seizures, and the electroencephalogram (figure 3E) showed fast and slow activity but no paroxysmal spikes.

Summary of Case 3. A six year old girl had the onset of myoclonic jerkings at age three and grand mal seizures at age four. After successful medical treatment for the seizures had been instituted, she gradually developed aphasia. Improvement in speech occurred with special instruction and additional medication, and seemed to be inversely correlated with the presence of generalized spike discharges in the electroencephalogram.

Case 4. A white female, the first of two children, was born in July 1948. There was no family history of convulsive or communication disorder. The pregnancy was uneventful. The labor was not considered abnormal, although there was a face presentation. Labor lasted 17 hours, with two hours of hard labor. The infant's general condition was good, although there was a slight swelling of the forehead.

She ate and gained weight well. She sat at six months and walked at 13 months. She was toilet-trained at two years. Speech developed during her second year, and she was able to say short sentences and said her prayers at night by the time she was three. The child suffered a fall without unconsciousness or evidence of serious injury when she was three and a half years old. A few months later in June 1952 the parents noted that she ceased to respond to calls, although she still talked well. Her ears were examined and were reported to be normal. During the summer her speech

gradually disappeared; understanding seemed to go first. For several days she was quiet and withdrawn, but there were no seizures of any kind.

In October 1952 she was hospitalized. Except for her difficulty in communication, physical examination showed no apparent abnormality. Hemogram and urinalysis were normal as was the skull roentgenogram. Electroencephalograms on several occasions revealed generalized spike wave discharges from all leads during most of the recording.* The child scored an IQ of 137 on the Merrill-Palmer test. It was felt that she displayed some negativism but that she was generally warm and affectionate and the examiners were impressed that she was well integrated in motor performance. It was noted that at times she appeared quite alert and at others somewhat confused. Some facial grimacing was also noted. At discharge from the hospital she was given Paradione for a trial period of two weeks.

The parents report that at the time of the patient's discharge from the hospital she said a few words but these disappeared again in a week or so. During the winter of 1952-53 the child seemed frustrated and was hard to manage, but did not withdraw from social contact. There was disagreement among many physicians as to whether she was deaf.

An electroencephalogram in June 1953 (figure 4A) again showed generalized spike wave discharges most prominent in the temporal leads. During 1953-54 she went to a school for the deaf. She did very poorly but there was no behavior difficulty. In 1954 she was seen by a neurosurgeon. Her electroencephalogram was unchanged except that the spike activity occurred "predominantly in the temporal lobes and more so on the right." Spinal fluid examination and pneumoencephalogram were entirely normal. Psychiatric evaluation was summarized: "The behavior would suggest psychogenic regression but its severity would equal childhood schizophrenia while her retention of warm affect is against that diagnosis."

Some time between 1952 and 1954 the child was placed on Dilantin medication possibly with some phenobarbital. For five or six days while she took these drugs she had spells during which her head shook toward the left and she was unsteady; afterward she was drowsy for an hour or so. The medication was stopped and except for the trial of Paradione she has taken no other anticonvulsant drugs.

The patient was first seen at the Central Institute for the Deaf in November 1954 at age six. She was exceptionally alert and friendly during the entire examination but showed no understanding of speech. She responded to spoken commands with a puzzled expression and a shrug of her shoulders or she ignored them completely. Little that was going on about her escaped attention.

*These records were shown by Dr. B. K. Bagchi at the meeting of the American Electroencephalographic Society, Atlantic City, N. J., 1956.

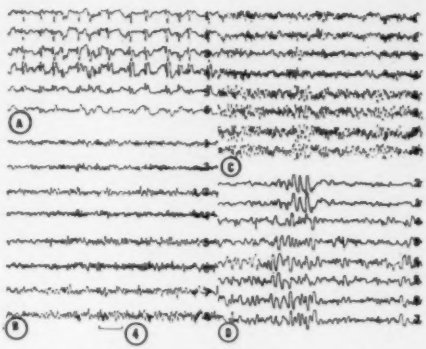

FIG. 4. Serial electroencephalograms in case 4 (*A*, *B*, and *C*) and single record in case 3 (*D*). *A*. June 24, 1953. *B*. April 18, 1956. *C*. September 19, 1956. *D*. April 1, 1955. Monopolar leads in *A*: 1, 3, and 5 are left frontal, vertex, and occipital leads; 2, 4, and 6 are homologous leads on the right. Other records are derived bipolarly, as in other figures.

She seemed to respond to an occasional sound but such responses were never repeated when attempts were made by the examiner to verify them. She played with noisemaker toys and seemed to enjoy them but she did not respond to their sounds when she was engaged in some other activity. On several occasions during the examination she seemed to respond to slight incidental noises, though most of the time she appeared completely oblivious to any sound including extremely loud noises. Because of this inconsistency of response, routine audiometric tests were not attempted. Indirect measurement of hearing was attempted through the conditioning of electrodermal responses to sound (EDR or PGSR), but it was virtually impossible to establish the conditioning on which this test depends. She named a few objects or pictures with poorly articulated words, although she showed no ability to understand them through hearing or lipreading. Her voice was high pitched and lacked natural quality and inflection, resembling the tone which is characteristic of some deaf children. Psychometric examination in November 1954 with the Advanced Performance Test yielded an IQ of 164.

She was enrolled in the Central Institute for the Deaf full-time classes for aphasic children in September 1955. By the end of her first semester in school she had begun to respond to sound quite consistently. She could write the letters for any individual speech sound spoken softly some distance behind her. By the end of her first school year of class work she had a speaking and understanding vocabulary of approximately 200 words. She could read and quickly memorize paragraphs of six or seven simple sentences and could answer simple questions on such paragraphs through both hearing and lipreading. Audiometric tests given in February 1956 showed normal threshold for

pure tones in both ears. In May 1956 near the end of her first year at the Central Institute for the Deaf she was given the Hiskey non-verbal test of learning aptitude and her LQ (learning quotient) was 102.[*]

Neurologic examination in March 1956 revealed a bright, friendly, hyperkinetic but cooperative child who was right-handed and left-eyed. She showed no neurologic deficit beyond her difficulty in communication. Vestibular response to caloric stimulation (40″ at 18° C) was within normal limits. An electroencephalogram taken in April 1956 showed a mild mixed fast and slow dysrhythmia without any spike discharges (figure 4B). This pattern persisted in September 1956 (figure 4C).

Summary of Case 4. An eight year old girl developed normally until several months following a minor head injury at age three and a half. She gradually became aphasic at age four, and during the same period of many months her electroencephalogram contained many generalized spike wave discharges. A few minor left-sided seizures occurred while she was taking Dilantin. Her communication has improved with intensive training in speech and language and with the spontaneous disappearance of the paroxysmal electroencephalographic discharges.

Case 5. A white female, the first of three children, was born in December 1943. There was no family history of convulsive or communication disorder. The pregnancy and labor were uneventful. The child fed well and gained weight properly. She sat at six months and walked at 13 months. By the time she was two or two and a half years old she was talking in short sentences. Her general development was good. Although her speech is said to have been "babyish" and one teacher suggested the possibility of a hearing deficiency, the first grade teacher stated that the patient had the best vocabulary in the class. There were no serious behavior difficulties and the child got along well with her contemporaries.

At the end of the first grade in 1951, about a month after recovery from the mumps, she lost the ability to respond to speech and noises. This occurred over a two-week period during which speech practically disappeared. She was given some intramuscular injections of vitamins. In two weeks speech and understanding had recovered. No seizure of any kind was noted at the time. Many consultants examined the child and most of them felt that she suffered from an "emotional block;" psychotherapy for both parents was undertaken on several occasions. The child's intellectual capacity was observed to be above average.

In the fall of 1951 the patient entered the second grade and did well until the end of that school year. Speech and understanding were lost again, more rapidly this time, in a day or so. She appeared generally well, although it was obvious that she was quite frustrated by her inability to produce anything other than "jabber noises." During this summer enuresis occurred.

She started in the third grade in the autumn of 1952, but she had little speech and hearing and her academic work was poor. She was not a disciplinary problem, however.

In the spring of 1953 she had a grand mal convulsion early one morning. Except for tiredness she was unaffected when she awoke. In May 1953 her physical examination was unremarkable and she seemed to hear. Ear, nose, and throat examinations and skull roentgenograms were normal. Several examiners were impressed with the possibility of a psychiatric disturbance. A generalized spike-wave dysrhythmia was observed in the electroencephalogram. After some difficulty in conditioning electrodermal responses to sound, it was possible to elicit responses within the limits of normal threshold. Mebaral medication was instituted and no more seizures have occurred.

The patient was first seen at the Central Institute for the Deaf in February 1954 at age ten. She did not speak or understand speech. There was no evidence of hearing during the entire examination. She behaved in an intelligent fashion and it was possible to communicate with her fairly well through writing. She read and followed correctly a number of simple written instructions, and was able to write answers to a number of simple written queries. She used one or two very poorly articulated words during the examination but clearly preferred writing to speaking. Near the end of the interview, she was sitting in a classroom where other aphasic children were being taught and appeared extremely interested in the class work. Her mother motioned to her that it was time to leave and the patient responded "you go, I stay." This was her only good speech and her only utterance of more than one word during the entire initial interview.

A few days later she entered the Central Institute for the Deaf classes for aphasic children. During her first few months in the school she relied heavily on writing for communication. She would often write for her teacher "I cannot hear" or "Talk is hard. I will never learn to talk." Occasionally she would write the question, "Why can't I hear?"

A conventional audiometric test was attempted two weeks after she began her schooling at the Central Institute for the Deaf, but her responses were too inconsistent for reliable evaluation.

[*]This represents a considerable difference from the I.Q. of 164 on the Advanced Performance Test administered earlier. There seems to be a rather consistent discrepancy between the scores on the Advanced Performance and the Hiskey for aphasic children (both congenital and acquired), whereas deaf children score more nearly the same on both tests. The major difference between the tests is that the Hiskey test is heavily weighted with memory items, particularly items requiring memory of sequences. Since the Hiskey test has been administered infrequently at the Central Institute for the Deaf, this observation has not been subjected to statistical evaluation.

In April 1954 she scored an IQ of 115 on the Advanced Performance Test. In December, after slightly less than two semesters in the school, a successful audiometric test showed normal thresholds of hearing. The test had to be administered carefully, however, for if two stimuli were presented in quick succession she became confused and her responses became erratic.

By January 1955 she had begun to progress rapidly. She was highly motivated and eager to improve her vocabulary and language. Those words which she knew could be spoken to her in a whisper. Those words which she did not know, she seemed not to hear at all. Her own report concerning words and phrases which she did not understand was that she did not "hear" them. Later she reported that when she first entered the Central Institute for the Deaf she had been able to hear music and noises but that when people talked it sounded like "blah, blah, blah."

Neurologic examination in March 1955 revealed a bright cooperative child, right-handed and right-eyed, without evidence of neurologic deficit other than the communication disorder. Vestibular responses to caloric stimulation (40″ at 18° C) were somewhat diminished. In April 1955 an electroencephalogram showed a mild slow dysrhythmia with paroxysmal bursts and temporal spikes during and after hyperventilation (figure 4D).

At the end of the 1955-56 school year, she could read, write, and converse with minimal difficulty. Her major remaining difficulty was in unfamiliar and abstract vocabulary.

During her fifth semester of special instruction at age 12 (March 1956), she was given the American Standard School Achievement Test and performed at the grade equivalent of 6.1. She entered grade seven in a public school in September 1956 and has done well.

Summary of Case 5. A 13 year old girl developed normally until age seven when she became aphasic for a period of two weeks. She was subsequently well for about a year when she became aphasic again, this time without immediate recovery. Her condition remained unchanged for another year when she had a single generalized convulsion. Since then, with special speech training and anticonvulsant medication, her recovery has been nearly complete.

DISCUSSION

After apparently normal acquisition of speech and language, all of these children developed aphasia for periods ranging from a day to several months. The symptoms then persisted from two weeks to several years. In addition, the children had a variety of convulsive manifestations: grand mal, partial, petit mal, and myoclonic seizures.

It does not seem reasonable to infer that this language disturbance is simply a variety of postictal Todd's paralysis, since there was poor correlation between the incidence of clinical seizures and the onset of the disorder of communication. Moreover, the convulsive phenomena that did occur before, during, or after the language disturbance were readily controlled medically or required no therapy (case 4). The degree of paroxysmal disorder in the electroencephalograms of these patients, however, did tend to correspond with the severity of language disturbance, although this relationship was not perfect. (For example, the electroencephalogram in case 1 was unchanged over the period of recovery from the first episode of aphasia.) The electroencephalographic disturbances were usually bilateral, often more prominent in the temporal leads. Temporal localization was also suggested by the focal character of many of the seizures and by the transient facial pareses seen in two patients.

Where there was lateralization of paroxysmal brain activity, the side more involved was not necessarily the same as that inferred to be "dominant" on the basis of handedness and eyedness. Roberts[5] has shown extensive data in adults that handedness and dominance for speech are, indeed, practically independent variables.

Although our patients show no evidence of structural brain lesions,[6] it may be suggested that persistent convulsive discharge in brain tissue largely concerned with linguistic communication results in the functional ablation of these areas for normal linguistic behavior. This thesis is supported by the good performances on non-verbal intellectual tests. No behavior similar to the clouded state of consciousness defined as "petit mal status" was seen. Further support is gained from the favorable course of the aphasic symptoms in these children. Although we believe that intensive speech training and anticonvulsant medication are both important in this improvement, there has been improvement from some episodes of aphasia with either form of therapy or with none.

The maintenance of normal or superior intellectual capacity in our cases helps to distinguish them from those with more malignant organic brain disease. The latter have probably not been seen in our series because our case finding agency is a school. Where language defect is an island of behavioral deficit, the distinction of acquired aphasia from a "primary" psychotic disorder is obvious. However, when the child has a regressive behav-

ioral reaction to the loss of communication, this separation may be difficult. The electroencephalographic disturbances among this group of aphasics are a useful differential cue.

Another problem is the differential diagnosis from peripheral deafness. Conventional audiometry is often impossible since aphasic children may respond to sounds in an inconsistent manner. Derbyshire's[7] method of electroencephalographic audiometry may be a more reliable testing procedure. In our experience, the presence or amount of hearing has often become clear only after a period of observation in the class room, playground, and dormitory.

SUMMARY

Five children are described who show a syndrome of acquired, largely receptive aphasia, sometimes recurrent, in association with some manifestations of convulsive disorder. Convulsions may be generalized, partial, myoclonic, or petit mal. The seizure manifestations have been readily controlled medically and are not closely correlated with the aphasic symptoms. In all cases a severe paroxysmal electroencephalographic abnormality, usually diffuse, is observed; electroencephalographic improvement tends to parallel improvement in speech re-education. General prognosis for these children is good with appropriate treatment.

ADDENDUM

A sixth case has come to our attention while this paper was in press.

Case 6. A nine year old girl without family history of convulsive disorder developed normally and was in the third grade. At age four there had been a single spell in which she fell limply unconscious and drooled. She was well until November 1956 when she complained of headaches and a vague visual disability. She could see but seemed to grope about. Examinations by physician and ophthalmologist were negative. One evening there were four brief tonic seizures 15 minutes apart. She was confused between spells and somewhat drowsy afterward. There were no residual symptoms immediately and she returned to school. During the next few weeks she gradually withdrew, had nightmares and temper tantrums, and had progressive difficulty "like stuttering" leading to absence of speech. Psychotherapy was instituted at this time; a variety of psychodynamic explanations for the symptoms were suggested.

In early January 1957 there was a single convulsive seizure involving the right face and also the right side of the body. She was then hospitalized. Physical examination, lumbar puncture, skull roentgenograms, and pneumoencephalogram were normal. Psychologic tests showed an IQ of 80 on nonverbal material. Psychiatric and psychologic consultants believed that the symptoms were psychogenic. Two electroencephalograms a week apart showed a prominent left temporal focus of high voltage 1 to 7 per second activity.

Examination at the Central Institute for the Deaf revealed a bright, friendly, cooperative child who seemed to enjoy the examination. She responded to both oral and written commands and could give reliable answers to questions requiring "yes" or "no" answers. There was no spontaneous speech. There was perseverative repetition of the syllable "um-m-m" on attempting to name pictures and objects. Her attempts to imitate words and syllables spoken by the examiner resulted in the same perseverative syllable. She could write a number of single words in response to questions such as "what color is your dress?" In some written words there was perseverative repetition of individual letters. She was discharged from the hospital without medication.

A month later her parents reported considerable improvement. At this examination she used speech, but in a telegraphic, poorly enunciated style. Often she could not say a word which she could write. Perseveration was still evident in both speech and writing. Imitation of sounds and words was still poor in spite of obvious effort. The electroencephalogram again showed the left temporal focus, but there were also generalized paroxysms of 3 to 6 per second waves, in some of which the voltage was higher on the right side. Shortly afterward anticonvulsant medication was instituted and improvement continued. The mother wrote in April 1957 that speech was as good as it had ever been and that the child had returned to school.

We are indebted to all those who generously shared their observations and records with us: Dr. Walter Moore, St. Louis University Medical School; Dr. Donald Thurston, Dr. Jean Holowach, and Dr. Irwin Levy, Washington University Medical School; Dr. James L. Wilson and Dr. B. K. Bagchi, University of Michigan Medical School; Dr. A. J. Derbyshire, Harper Hospital, Detroit; Dr. Robert S. Knighton, Henry Ford Hospital, Detroit; Dr. Samuel Livingston, Johns Hopkins Hospital, Baltimore.

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Transient Astereognosis Induced by Intravenous Barbiturates

Robert Jaffe, M.D.

IN CLINICAL TERMINOLOGY, stereognosis is defined as the ability to recognize physical qualities and identity of three-dimensional objects by palpation.[1] Astereognosis, accordingly, is defined as a defect in this ability, characteristically unilateral. These definitions have been refined, altered, and qualified in various ways by many investigators. Critchley[1] has reviewed them in great detail.

The most commonly accepted theory attributes astereognosis to a defect in *gnosis,* or tactile memory, produced by lesions of the parietal lobe. In terms of this theory, the parietal lobe is considered to have the special function of elaborating and integrating the information derived from the somatosensory afferent system with the "engrams" laid down by prior experience.[2] The integrity of the parietal cortex is, therefore, considered essential for proper tactile recognition, and astereognosis is presumed to occur when a lesion is present in that area.

The second approach to the problem of astereognosis questions the very existence of *gnostic* functions. In this view, astereognosis is attributed to defective functioning of the afferent system itself, that is, to the lack of sufficient information to allow for distinguishing the physical characteristics of the objects. In many cases, sensory defects may be enhanced by depression in general mental function.

Most of the evidence for the above theories is derived from clinical-pathologic correlations. In such studies, it is usually implied that the observed behavioral abnormalities are static, and they are equated with the undeniably static lesions seen at autopsy. The behavior of the living patient, however, is never static. The more complex the behavior, the more it tends to fluctuate, thus indicating the diversity of the factors which influence the symptom pattern. One may observe fluctuation under controlled conditions, as by the use of intravenous barbiturates. This method has been used successfully in the study of disturbances in orientation and speech,[4] motor function,[5] eye movements,[5a] and some aspects of sensory function.[5b] It would seem, therefore, to be of value in studying special somatic sensation, since barbiturates (in the presence of brain disease) seem to bring out latent defects in function or to intensify defects already present.

In a previous study[6] involving a large series of cases of astereognosis, there were some cases in which spontaneous fluctuation took place and in whom astereognosis was present or absent according to the severity of the sensory defects and the mental state of the patient. The present study was designed to test the hypothesis that astereognosis may be due to a combination of defective afferent functions rather than to location and degree of underlying brain pathology. For this purpose, selected patients were examined first under normal conditions and later while under the influence of intravenous barbiturates.

Case 1. A 22 year old man was admitted to the Third Division Neurology Service of Bellevue Hospital for investigation of his convulsive disorder. Since the age of five, the patient had suffered from infrequent grand mal seizures. These seizures invariably began with an "aching sensation" in the sole of the right foot. This sensation would spread to involve the entire right foot and leg, following which the patient would lose consciousness and have a generalized convulsion. The seizures occurred at intervals of two to three months, in spite of the fact that the patient did not take medication, led a very irregular existence, and was a heavy drinker.

General physical examination revealed no abnormalities. The patient was alert and oriented for time, day, date, and place. He was cooperative and showed no confabulation, denial of illness, displacement, or reduplication of the hospital. He gave normal responses when tested by the method of double simultaneous stimulation (face-hand test[7]).

Cranial nerve function was normal. Perimetric fields were full. There were no abnormalities in motor function other than a questionable minimal difficulty with fine manipulation using the right hand. Perception of light touch, pin-prick, vibration, position, and passive motion was normal in all four extremities. Familiar objects (screw, small safety pin, die, marble, paper clip, penny, nickel, and dime) were correctly identified in either hand and in both simultaneously.

Minimal abnormalities in sensation were shown in the following tests: 1) Two-point threshold at tip of middle finger, 6 mm. on right, 3 mm. on left; on dorsum of foot, 33 mm. on right, 21 mm. on left. 2) Minimal errors in touch localization in right hand and foot. 3) Decreased adaptation time

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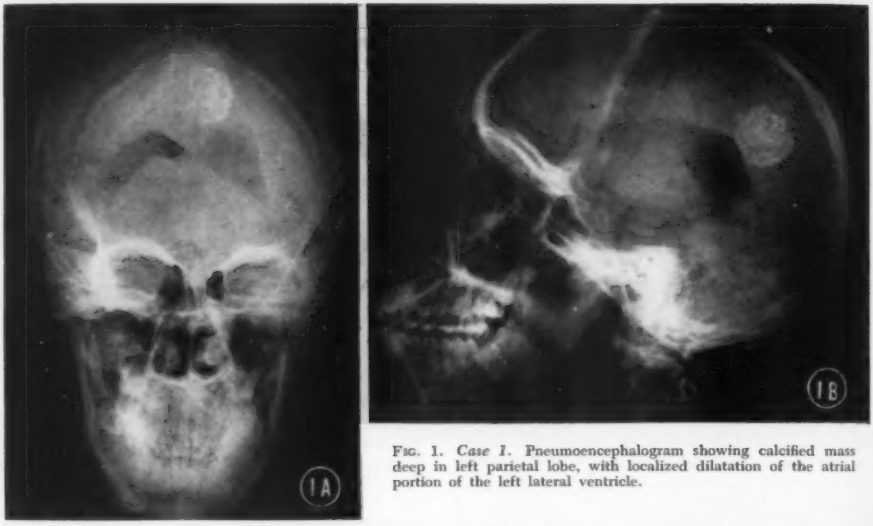

FIG. 1. *Case 1.* Pneumoencephalogram showing calcified mass deep in left parietal lobe, with localized dilatation of the atrial portion of the left lateral ventricle.

to pin-prick. This could be elicited in the right hand only by the method of double simultaneous stimulation,[8] but was demonstrated when the right foot was tested alone.

Laboratory findings included a positive blood Mazzini test but a negative Wassermann reaction. The cerebrospinal fluid was clear and colorless and had a protein of 35 mg. per cent. It contained no cells and the colloidal gold reactions were normal. Electroencephalograms were normal on two occasions. Roentgenograms of the skull revealed the presence of a round dense calcification 2.5 cm. in diameter, deep in the left parietal parasagittal region. Pneumoencephalogram revealed marked dilatation of the atrium and posterior horn of the left lateral ventricle (figure 1).

The patient was given a slow intravenous injection of sodium Amytal. After 0.4 gm. had been given, he had marked nystagmus and was drowsy and dysarthric. He was oriented for date, but misidentified the hospital, confabulated a previous interview with the examiner, and showed bilateral extinction on the face-hand test by the method of double simultaneous stimulation. At this time the patient had a definite right lower facial weakness and a marked drift of the right upper extremity. Detailed sensory examination could not be performed, but the patient was tested for stereognosis. He was unaware of, or unable to identify, objects placed in the right hand, but at the same time was able to recognize a marble, die, and pencil stub held in the left hand. Within two minutes the patient was fully oriented and able to identify objects in either hand.

Case 2. A 50 year old man was admitted to Mt. Sinai Hospital for investigation of a progressive left hemiparesis of several months' duration. This hemiparesis was most marked in the lower extremity and had only recently spread to involve the upper. There were no associated complaints.

General physical examination revealed no abnormalities. The patient was oriented in all respects. He showed no tendencies toward denial of illness. An incomplete left homonymous hemianopsia could be demonstrated by the method of double simultaneous stimulation.[9] Cranial nerves were otherwise normal. There was marked weakness of the left lower extremity, with increased reflexes and extensor plantar response, and slight drift of the extended left upper extremity, but no difficulty in coordination or fine movements with the left hand.

Sensory defects were also much more marked in the left lower extremity. Light touch was not perceived over the left foot, but was normally perceived in the left hand. There was slight hypalgesia to pin-prick over the left foot. Position sense was defective at left toes, fingers, and wrist. Vibration was normally perceived. Two-point threshold was 5 mm. on the tip of the left middle finger, 3 mm. on the right; 150 mm. on the dorsum of the left foot, 60 mm. on the right. Figure-writing was equally well perceived on either palm. Adaptation time to pin-prick was reduced in the left hand (but only when tested by the method of double simultaneous stimulation). There was extinction of stimuli applied to the left hand simultaneously with stimuli applied to either the homolateral or contralateral cheek or foot.

Tactile identification of the same series of objects judged by case 1 was performed without error in both hands, singly and simultaneously.

The patient was given 0.25 gm. sodium Amytal by intravenous injection, became dysarthric, de-

veloped nystagmus, and denied knowing the names or occupation of the examiners. A left homonymous hemianopsia was present. There was marked weakness of the left upper extremity and paralysis of the left lower. He was unable to identify a pencil stub, marble, safety pin, watch, or coins held in the left hand, while at the same time these objects were readily identified with the right hand.

A right parietal parasagittal meningioma was totally removed at operation. When examined 48 hours after operation, the patient was fully oriented and showed no denial of illness. Although the left hemiparesis was slightly increased as compared to the preoperative status, sensation had improved in many respects. Position sense was still defective in the left hand and foot, but two-point thresholds were equal on the two sides, there was no extinction on double simultaneous stimulation, and stereognosis was normal.

Case 3. A 44 year old man had had a partial removal of a right frontoparietal glioblastoma, followed by a course of radiotherapy in March 1955. He was re-admitted to the Mount Sinai Hospital in a comatose state on May 14, 1955. He responded well to a second course of radiotherapy and was ambulatory when examined on June 1, 1955.

He was oriented for time, place, day, and date but denied having the left hemiparesis and left homonymous hemianopsia, which were grossly apparent to the examiner. Sensation was normal to all modalities on the right side, while the left showed defects in perception of touch, pin-prick, position, and passive motion. Two-point threshold was 18 mm. on the tip of the left middle finger, 3 mm. on the right. Point-localization and graphesthesia were defective on the left hand. Double simultaneous stimulation revealed consistent displacement of touch stimuli to the left hand when the contralateral face or foot was touched. Pin-prick adaptation time was reduced in the left hand.

A slight defect in stereognosis with the left hand was manifested on the first trial, with the paper clip being identified as a "safety pin," and the nickel as a "flat metal object." On subsequent trials all objects were correctly identified.

This patient was given 0.3 gm. sodium Amytal intravenously. He became drowsy and developed nystagmus and dysarthria. At this time he showed a marked increase in his left hemiparesis. On testing for stereognosis, he gave "I don't know," or "pencil" responses to all objects placed in the left hand; he correctly identified a safety pin, pencil stub, die, coins, pocket watch, and examiner's finger placed in his right hand.

Case 4. A 56 year old man was admitted to the Mount Sinai Hospital complaining of "confusion, inferiority complex, and trouble with speaking." These complaints were of two years' duration and had become progressively worse. There were no complaints of visual, motor, or sensory deficit.

On examination the patient was found to be anxious, depressed, and tearful. He appeared bewildered. Although oriented for time, place, and person, he showed marked defects in recent and remote memory. There was severe right-left confusion, with inability to cross the midline on command. On double simultaneous stimulation (face-hand test) he showed extinction of stimuli applied to either hand, even when this test was performed while the patient's eyes were allowed to remain open. There was no evidence of aphasia. Examination of the cranial nerves was essentially negative. The visual fields were full. Motor function and reflexes were normal.

Perception of touch, pin-prick, and vibration was normal on the face and all four extremities. On testing of position sense in the fingers and wrists, the patient showed a gross defect, giving confabulatory responses. He was able, however, to handle small objects in either hand without difficulty. Normal responses were obtained in testing position in the toes. Two-point threshold was 4 mm. on the tip of each middle finger. Point localization was grossly normal. On testing for graphesthesia over the palms, there were about 50 per cent errors on each hand. Responses on testing for adaptation to pin-prick were normal and equal on the two hands. The standard series of familiar objects was readily identified in either hand.

A pneumoencephalogram showed a moderate degree of diffuse cerebral atrophy.

In view of the patient's pronounced depression and anxiety, a therapeutic trial of electroconvulsive therapy was carried out. The first treatment was performed by the "focal" technic,[10] with one electrode in the right frontal region and one in the right parieto-occipital region, narcosis having been induced with 0.25 gm. sodium Pentothal given intravenously in 2½ per cent solution.

As the patient began to respond a few minutes after the end of the treatment, he had a severe left hemiparesis, a left homonymous hemianopsia to double simultaneous stimulation, and extinction of touch and pin-prick stimuli on the left extremities on simultaneous stimulation of the corresponding part of the right side.

Ten minutes later the left hemiparesis was still present, although less severe. Orientation was not grossly defective. The visual field defect and extinction phenomena were unchanged. The patient was unable to identify objects placed in his left hand, while those in his right hand were correctly identified. Within 20 minutes of the end of the treatment, the only residual focal sign was a very mild left hemiparesis. Stereognosis at this time was normal.

DISCUSSION

The cases cited above provide unequivocal examples of astereognosis. Under "normal" conditions of testing, tactile shape identification was well performed. Under the experimental conditions, multiple focal sensory deficits were induced or aggravated and tactile shape identification became impossible.

Superficially, at least, one may postulate a purely quantitative relationship wherein the

patient under "normal" circumstances obtains the minimum necessary amount of information with which to perform stereognosis. The barbiturate might then act either by reducing the amount of information received and/or by lowering the capacity of the already compromised cerebral tissue to integrate this information.

The conditions of testing, unfortunately, do not permit a very detailed study of the component dysfunctions. The barbiturate narcosis is difficult to maintain at a level at which cooperation in a detailed sensory status may be obtained. Many patients with brain disease showed marked "withdrawal" responses,[12] becoming completely mute even with small doses and while still evidently awake. Other patients may still respond verbally at normal dose levels, but show little or no increase in focal signs almost until the level of absolute hypnosis is reached. The patients cited in this paper actually represent a minority of the patients tested by this method. Ten other patients who showed minimal or moderate unilateral sensory dysfunction (and normal stereognosis) under normal conditions fell into the "untestable" or "no effect" groups after the intravenous injection of sodium Amytal. Even this small number of positive cases seems to illustrate the point that alteration in function, without further change in the structural lesion, may account for the presence or absence of astereognosis.

These cases also illustrate the corollary point that the exact locus of the lesion may be less important than the amount of functional deficit present. Case one had an apparently static lesion deep in the parietal lobe. Case two had a relatively benign expanding lesion causing external compression of the parietal lobe, and case three had a highly malignant lesion which probably involved the white matter of the anterior and middle portions of one hemisphere. The degree of sensory dysfunction present during the control examination varied, but the common factor with these three patients was that all showed a marked increase in focal signs following the injection of sodium Amytal.

Case four presents an even clearer demonstration of this point, since this patient did not have any "focal lesion" at all, in the ordinary sense of the term. The transient unilateral sensory-motor syndrome in this case was a postictal phenomenon caused by whatever diffuse and transient effects electroconvulsive therapy has on cerebral tissue.

The results of the present study tend to support the view that astereognosis is not a unitary defect, but one attributable to deficiencies in information derived from many modalities. Under the conditions of this study, the critical factor in the induction of the symptom of astereognosis appeared to be the degree of deficit in sensory function present, rather than the locus, nature, or severity of the existing organic lesion itself.

SUMMARY

Comprehensive sensory examination was performed on 13 patients with unilateral brain lesions. All patients showed some degree of defect in somatic sensation. None showed astereognosis. Patients were given intravenous barbiturate and re-tested for astereognosis.

The findings are discussed in terms of the theories of kinesthetic object identification. It is concluded that astereognosis may not be, under ordinary circumstances, a unitary deficit due to the presence of a focal lesion in the parietal lobe, but rather a manifestation of a complex dysfunction in sensory input, with or without the additional factor of a disturbance in the level of consciousness.

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Sequelae of Western Equine and Other Arthropod-Borne Encephalitides

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THE SEQUELAE, both clinical and pathoanatomic to type A encephalitis (von Economo's disease or lethargic encephalitis) are well known and have been the subject of extensive investigation. However, the sequelae to the North American arthropod-borne type B encephalitides (western equine encephalitis, St. Louis encephalitis, and eastern equine encephalitis) remain incompletely studied. At the present, not only must much be learned regarding the nature of the long-term manifestations in these diseases, but the lack of adequate information concerning the pathoanatomic basis for these sequelae is particularly evident.

In this report the pathoanatomic findings in a confirmed case of western equine encephalitis in its chronic stage will be recorded. This is apparently the first such report. In order to evaluate this case in the light of reports concerned with the clinical sequelae and the acute pathology of this disease, we made an extensive search of pertinent literature dealing with the various forms of the arthropod-borne type B encephalitides. Such reports were found to be widely scattered, and no adequate review of these subjects was encountered.

CLINICAL FEATURES OF SEQUELAE

A comparison of the reports of sequelae which have appeared in the literature is beset with certain difficulties. First, there has been considerable variation in the criteria for diagnosis in the cases comprising these reports, especially so among those reports made prior to the past decade, for only in recent years have criteria for diagnosis been crystallized. At the present time the sole basis for a clinical diagnosis in any given case, other than the actual isolation of the viral agent, is the serologic demonstration of a significant rise or change in antibody titer.[1–4] This followed early surveys in which antibodies were found repeatedly in normal control subjects, first to the virus of St. Louis encephalitis,[5–7] and then to the virus of western equine encephalitis.[7–9] Later, improvements in technical methods, particularly the development of practical acute and convalescent serologic tests, permitted more feasible differentiation between what must be interpreted as a previous "exposure" to the virus, as against active infection. In the light of these more rigid criteria, many of the earlier reports, in which a single positive neutralization test was usually the basis of the diagnosis, should now be considered as a series of "presumptive" cases. Only in the current extensive investigations of Finley and his group[10,11] of the California epidemics and in that of Mulder and associates[12] for a smaller Colorado epidemic have large series of cases been composed of "proved" cases only.

It was also apparent that the criteria used for including cases as sequelae varied widely from report to report, or in some series was not even stated. Therefore, it was found necessary for purposes of tabulation to consider only "major sequelae," that is, instances of unquestioned neurologic disorder or deficit and/or cases with definite mental deterioration or retardation. Finally, there was considerable variation in the methods employed for follow-up of the cases. In some there was a direct examination by a single examiner; in others, questionnaires sent to local physicians constituted the follow-up procedure. Particularly, the interval of time elapsed since the initial infection varied. In regard to the latter, Finley and associates[10,11] have stressed the frequency of complete recovery from or at least substantial improvement in many of the sequelae observed early in the course of the disease. This was particularly so when follow-up observations were continued past the first year.

Despite these shortcomings, it was thought valuable to attempt an evaluation and tabulation of these reported studies, and that perhaps a better understanding of the general problem would thus result. In table 1 are tabulated all reports known to us,* in which series of cases were followed to observe the occurrence of sequelae to the three North American arthropod-borne encephalitides.

From the laboratory of neuropathology of the Langley Porter Clinic, the departments of psychiatry and pediatrics of University of California School of Medicine, San Francisco, and Porterville State Hospital, Porterville, California.

*Three other papers[13–15] dealing primarily with isolated instances of sequelae to western equine encephalitis, are not listed in this table because of the limited number of cases followed.

TABLE 1
INCIDENCE OF "MAJOR SEQUELAE" IN ARTHROPOD-BORNE VIRUS ENCEPHALITIS

Authors	Year	Epidemic	Year	Diagnostic Method*	Follow-up Period	Total Cases	Major Sequelae Number	Major Sequelae Per Cent
EASTERN EQUINE ENCEPHALITIS								
Ayers & Feemster[35]	1949	Massachusetts	1938	Single	9 yr.	8	6	75
Dent[42]	1955	Louisiana	1947	Single	2 yr.	2	0	0
ST. LOUIS ENCEPHALITIS								
Bredeck et al. [17]	1938	St. Louis	1933	Clin.	3 yr.	331	3	1
Finley et al.[10]	1955	California	1952†	Rise	3-7 yr.	132	10	7.7
Palmer & Finley [11]	1956							
WESTERN EQUINE ENCEPHALITIS								
			1937					
Howitt[38]	1939	California	1938	Single	1 yr.	20	3	15
McGugan[19]	1942	Alberta	1941	Single	1 yr.	23	3	13
Adamson & Dubo[20]	1942	Manitoba	1941	Single	1-3 mo.	55	0	0
Davison[21]	1942	Saskatchewan	1941	Single	8-10 mo.	33‡	7	21
Medovy[22]	1943	Manitoba	1941	Single	3-7 mo.	17§	4	24
Mulder et al.[12]	1951	Colorado	1949	Rise	6-8 mo.	25	9	36
			1940					
Fulton & Burton[25]	1953	Saskatchewan	1952	Single	5-10 yr.	101	10	10
Finley et al.[10]	1955	California	1952†					
Palmer & Finley [11]	1956			Rise	3-7 yr.	362	30	14
Totals (western equine encephalitis)						636	86	13.5

*Diagnostic Methods:
Single—Single serologic titer only
Clin.—Clinical studies only
Rise—Rise in serologic titer

† Cases from 1945-1950 also
‡ Only cases 13 years and under
§ Only infants studied

Sequelae of Western Equine Encephalitis

Incidence. The initial epidemic of St. Louis encephalitis (1933) was associated with a relatively low rate of sequelae.[16,17] With the advent of the great epidemics of western equine encephalitis in 1941 in North Dakota, Minnesota, and the adjacent Canadian provinces of Manitoba and Saskatchewan (2,792 cases[18]), and the subsequent recurrent epizootics of the California Central Valley, particulary those of 1950 and 1952, it soon became evident that sequelae could be expected more frequently after this particular infection.[19–22]

When major sequelae to western equine encephalitis from these and other reports are tabulated (table 1), a range of 10 to 36 per cent in the incidence of sequelae is evident. Moreover, with regard to the entire series of 636 reported cases, 86, or 13.5 per cent, had developed major sequelae. These consisted of such common neurologic manifestations of brain damage as states of quadriplegia, hemiplegia, and spasticity or rigidity. Mental retardation or deterioration, alone or in conjunction with the above motor residua, was also a common result. While it has been noted[11] that many of the minor sequelae and subjective complaints improve with time, it would seem safe to assume that these major sequelae would persist. Thus the figure of 13.5 per cent may represent a fair estimate of the incidence of sequelae to be expected among cases of infection with western equine encephalitis.

Age distribution. An unusual characteristic of western equine encephalitis infection is the apparent increased susceptibility of infants under one year of age and the frequency of sequelae in this age group. In spite of earlier reports to the contrary[6] (and as a result, some confusion on this point in later reports), evidence that these infants are more prone to western equine encephalitis infection has since been shown repeatedly. Donovan and Bowman,[18] in a study of the large-scale 1941 epidemics in mid-western United States and Canada, demonstrated an attack rate of 200 per 100,000 in infants under one year of age, as against a rate of 55 per 100,000 in the population at large. Again, of 174 laboratory-confirmed cases from the California epidemics of 1945 through 1950, Lennette and Longshore[24] found that 20.1 per cent of these cases had occurred in infants under one year. Similarly, Hollister and associates,[25] in summarizing their experience in the entire 1945-1952 period in California, noted an attack rate of 375 per 100,000. This compared with rates of 10 to 50 per 100,000 population in the other age groups.

When the cases reported and tabulated in table 1 were divided as to age into two groups, those under one year and those over one year, it was found that not only did the infants under one year experience a disproportionately high attack rate, representing 27 per cent of the cases, but this group was found to have de-

veloped 54 per cent of all the major sequelae reported. Furthermore, among this group of 137 infants, there were 41 instances of sequelae, or an incidence of 30 per cent. This compared with the rate of 13.5 per cent for all ages and with an incidence of 10 per cent among the group over one year of age.

Noteworthy was the increased severity of the sequelae occurring in infants,[15,21,22] especially in those less than three months of age.[10,11] The neurologic residua in these infants, while commonly characterized by severe states of quadriplegia, spasticity, or rigidity, were particularly associated with recurring convulsive states and with severe mental retardation.

Incidence of parkinsonism. With the knowledge that parkinsonism was the major sequela of lethargic encephalitis, clinicians early in their observations on the St. Louis epidemic of 1933 and the western equine encephalitis epidemic of 1941 were on the alert for the development of parkinsonism following these diseases. This syndrome was not conspicuous in initial observations.[26,27] However, more recent reports would indicate increasing evidence for the prominence of parkinsonism as a sequela of western equine encephalitis infection in the older age group. Of particular importance is the observation of Palmer and Finley[11] that this state may develop after a latent, symptom-free period of two to three years. Ten cases of parkinson-like state (six of Mulder and coworkers,[12] two of Fulton and Burton,[28] and two of Palmer and Finley[11]) were found among the 86 sequelae in these series of cases, an incidence of 12 per cent. The sequela assumes even more importance when infants were excluded from the tabulation, since a parkinson-like state was found to occur in 30 per cent of the older group.

Psychologic sequelae. The majority of reports list personality changes prominently among residua of both western equine and St. Louis encephalitis. Although the greater share of these subside within the first year or two, reports of more persistent personality changes and of intellectual deterioration in adults have been made. In a careful psychologic evaluation after an unusually severe epidemic in Colorado, Mulder and his associates[12] noted severely impaired intellectual functioning in six of 22 adults followed. Particularly affected were such higher intellectual functions as abilities for abstract thinking, for planning, and for the development of new ideas. Fulton and Burton[28] and Palmer and Finley[11] noted a gradual and progressive course in the intellectual deterioration in adults so affected, frequently after a latent period. In addition, the former writers concluded on the basis of serologic studies that mental institutions harbor numbers of patients whose deterioration may be solely the result of subclinical infection with western equine encephalitis.

Sequelae of Eastern Equine Encephalitis

Epizootics, the result of the virus of eastern equine encephalitis, have been rather limited both in geographical extent and in the numbers affected. Epidemiologically, this may apparently be related to avian host ecology[29,30] and to the general absence of an appropriate vector for man.[31,32] Thus, only two small-scale epidemics have occurred, that in Massachusetts in 1938 and the more recent Louisiana outbreak (1947). Characteristically, these epidemics have occurred among infants and children predominantly, with a high mortality (approximately 75 per cent) and with the occurrence of sequelae among the majority of survivors.[33] Sequelae were virtually universal and of severest degree among infants under one year of age, and resulted in gross neurologic states of hemiplegia and spasticity and mental retardation. However, it has become evident that milder cases do occur, particularly in adults, and apparently of a subclinical type without residua. This has been demonstrated by reports of the presence of neutralizing antibodies in endemic areas in Louisiana[31] and in the Dominican Republic.[29]

Sequelae of St. Louis Encephalitis

In comparison to western equine encephalitis and eastern equine encephalitis, infection with St. Louis encephalitis is associated with a generally lower incidence of major sequelae (1 per cent[17] to 7.7 per cent[10,11]) (table 1). Moreover, in contrast to the first two infections (vide supra), infants under one year of age are affected infrequently by the virus of St. Louis encephalitis; for example, they constituted only 0.6 per cent of cases in the St. Louis epidemic of 1933.[34] Similar low morbidity rates were noted in the subsequent California epidemics of St. Louis encephalitis, with only 1.4 per cent of the cases reported being under one year.[24,25] Likewise, the absence of sequelae in this age group is striking. It has been suggested,[24,25] that this decreased susceptibility in the infant is related to a more widespread immunity to St. Louis encephalitis and the transfer of protective maternal antibodies to the newborn, but this does not appear to be the sole or possibly even the main factor.

CLINICOPATHOLOGIC REPORT*

The patient was a five year old boy who was born June 4, 1950 at Merced in the heart of the Central Valley of California. Pregnancy, labor, and delivery were without untoward event. At birth, he breathed immediately and no abnormalities or injuries were evident. His early development proceeded normally until the onset of an illness on July 4, 1950, at the age of one month. At this time the first large epidemic of western equine encephalitis was rampant in the valley.[24] The onset of the illness was characterized by irritability and the passage of a moderate number of liquid stools. Fever of 102° to 104° rectally ensued, and 12 hours after the onset of the illness episodes of rigidity developed. These became more frequent and were accompanied by a position of opisthotonus. Forty-eight hours after the onset of the illness, July 6, the infant was admitted to the University of California Hospital.

On admission the infant was semiconscious, appeared limp, and occasionally jerked his right arm. He kept his head turned to the right. His legs were mildly spastic but the reflexes were normal. A faintly turbid fluid was obtained on lumbar puncture. It contained 270 white blood cells per cu. mm., with 46 per cent polymorphonuclear leukocytes and 54 per cent lymphocytes. The protein content was 150 mg. per cent. There was no growth on culture.

The hospital course was stormy, but with gradual remission of symptoms over a three-week period. Serologic viral studies were carried out by the California State Department of Public Health Viral and Rickettsial Disease Laboratory in Berkeley (table 2). These tests showed a conclusive rise in antibody titers exclusively against the virus of western equine encephalitis during the course of the illness and a fall in titer one year later. Particularly diagnostic was the nature and magnitude of the rise in complement-fixing antibodies.

Shortly after hospital discharge (August 3, 1950), no significant level of retardation was evident. However, by six months of age, he was found to be unable to sit without support, unable to roll over, and he could not raise his head when prone.

At examination at one year, while his motor abilities had advanced, having achieved sitting ability and prehensile movements, adaptive and language behavior were at 28-week levels. A mental age of seven months and an approximate I.Q. of 60 were assessed. Neurologically, there were increased deep reflexes in the right lower extremity.

At the age of 16 months, he sustained his first grand mal epileptic attack which was initiated on the right side. At this time an electroencephalogram showed consistently higher than normal potentials, with greater abnormality in the leads from the right hemisphere. On pneumoencephalography, the right lateral ventricle was observed to be minimally dilated and the subarachnoid spaces on the right slightly enlarged.

He was reexamined at two years. It was reported that walking had been achieved at 18 months, and that restlessness and hyperactivity had become a problem. In the interval, two seizures had occurred in association with febrile illnesses. The child walked awkwardly and there was increased tone in his right hand. He had no language ability and was hyperactive, inattentive, and destructive. Motor abilities were most advanced and an approximate mental age of nine and a half months was assigned, or a numerical I.Q. of 40. At two and a half years, his behavior was relatively unchanged. During the following two years he became subject to seizures occurring two to three times per month. His hyperactive and destructive behavior had increased to the point that institutionalization was recommended.

He was admitted to a state hospital shortly before five years of age. On examination he was hyperactive, without speech, and showed a scissors-type gait, poor coordination, and increased deep reflexes. He developed an enterocolitis due to *Shigella flexner* and failed to respond to a seven-week course of treatment. He had five seizures during the first month of the illness, but none thereafter. His condition deteriorated steadily and his weight fell to 27 pounds. Death resulting from inanition occurred on July 7, 1955 at the age of five years.

NECROPSY

There were no gross changes in the internal viscera. Histologic examination revealed only a capillary hyperemia of the lungs and a mild fibrosis and lymphocytosis of the portal spaces of the liver. The latter findings were interpreted as reflecting the prolonged enterocolitis.

Gross Observations in the Brain

The brain was small, weighing 815 gm. after formalin fixation. The left hemisphere showed

*This case was the subject of a more detailed clinical report by Bruyn and Lennette,[15] as their case 2, at which time the child was two and a half years old.

TABLE 2

SEROLOGIC STUDIES AGAINST VIRUS OF WESTERN EQUINE ENCEPHALITIS*

(Case Report)

Test	7-11-50	7-21-50	8-3-50	10-5-51
Complement-fixation	<1:8	1:64	1:256	1:64
Virus neutralization	400 LD_{50}		5000 LD_{50}	1100 LD_{50}

*Serologic tests for St. Louis encephalitis, lymphocytic choriomeningitis, and mumps were negative. The mother of the patient had negative titers to these infections and to western equine encephalitis.

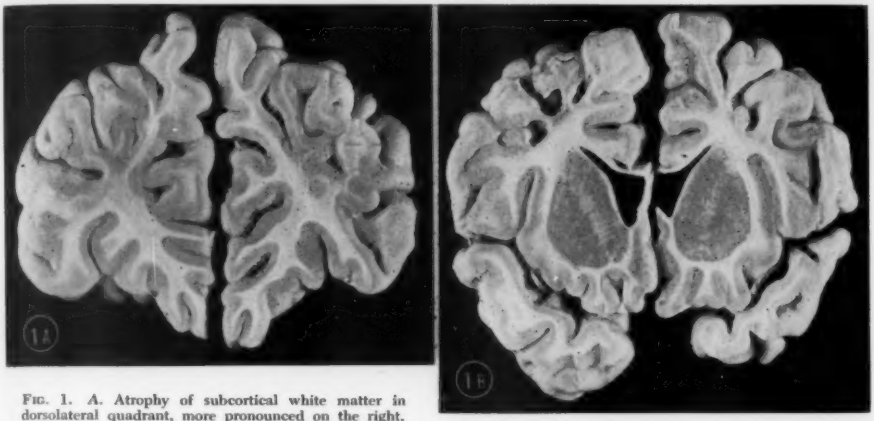

FIG. 1. *A.* Atrophy of subcortical white matter in dorsolateral quadrant, more pronounced on the right, sides reversed. *B.* The subcortical involvement encroaches on sulcal troughs, ballooning them. Gyral crests and the central white matter remain preserved. Severe on right, sides reversed.

greater reduction and weighed 387 gm. as compared to a weight of 428 gm. for the right hemisphere. There were normal lobar proportions and the convolutional pattern was well differentiated. The gyri did not appear atrophic, but they were small, apparently from a tendency for "crowding." This was most pronounced in the lateral aspects of the frontal and parieto-occipital regions. The leptomeninges were thin. The basal vessels were delicate. The brainstem and cerebellum appeared to be of proportionate size and revealed no external changes. A midsagittal section revealed fairly severe generalized atrophy of the corpus callosum. In coronal sections through the most anterior part of the frontal lobes there was symmetric, moderate demyelinization and atrophy of the white matter which was restricted to the dorsolateral quadrants (figure 1A). In relation to these areas of white matter changes, there was occasional involvement of the cortex confined to the troughs of sulci. At levels of the anterior parts of the basal ganglia (figure 1B), there was similar white matter atrophy confined again to the dorsolateral quadrants, but the cortical atrophy had extended. Here, the troughs and sides of sulci were so severely destroyed that the relatively preserved gyral summits appeared as "mushroom-like" caps. This was most severe on the right. A similar process was observed in the parietal lobes. Here, the atrophy was most severe in the areas surrounding the posterior part of the interparietal sulcus, much more severe on the left than on the right. The anterior and lateral parts of the thalamus appeared to be atrophic, being discolored and unusually firm. Ammon's horn was reduced in size bilaterally. The ventricles were diffusely enlarged to a moderate degree, in relation to the areas of atrophy.

*Microscopic Observations in the Brain**

Microscopically, the pathology might be viewed as having two components, an inactive and an active process. The first consisted of destructive and demyelinated scars (figure 2). These were fairly well delimited to the subcortical and gyral white matter, corresponding in distribution to those areas noted previously in the gross description. The cortex was uninvolved, except where the underlying white matter was affected most severely. In these areas, the pattern produced could be likened to a "U," in which the trough of a gyrus was most severely involved, whence the process extended laterally to encroach on either side of the sulcus. It is to be emphasized that the above changes of white matter and cortical involvement were circumscribed and that other parts of the brain were completely intact.

Of the subcortical ganglia, the thalamus was the most severely affected. Foci of atrophy were found in the nucleus ventralis anterior and in the nucleus medialis dorsalis. A few small foci were found in the midputamen region. There were no lesions in the remaining basal ganglia, or in the subthalamus, hypothalamus, brainstem, cervical cord, and cerebellum.

Histologically, the scars were essentially similar in all involved areas. They were locally destructive, affecting nerve cells and fibers equally. They were predominantly composed of dense glial fibers, but also contained scattered fibrillary astrocytes and a moderate number of minute neutral fat deposits in gitter cells. There was neither collagen nor reticulin proliferation within the scars. Basophilic staining deposits or "calcifications" were abundant, either in the form of focal plaques, linear streaks, or minute granules.

There were differences in the pattern of the lesions, depending upon whether they were in the cortex and white matter or in the thalamus.

*With the technical assistance of Irene Robley.

Cortical white matter lesions. The lesions in the cortex and white matter were intimately related but variable in degree, thus disclosing three different patterns.

A. Mild. Here the effect appeared to be primarily on the subcortical white matter (figures 2A and D). The overlying cortex was surprisingly free of change, with the exception of a mild marginal gliosis, and that appeared to be confined to the troughs of sulci. The subcortical white matter was equally involved in crests and troughs of gyri. The central white matter was entirely unaffected. The "calcifications" in these lesions were distributed as linear streaks and plaque-like foci, generally in the centers of these scars (figure 3A).

B. Moderate. The pattern differed from the former in that it encroached on the overlying cortex. This tended to occur only where the white matter was most extensively involved, here favoring the sulcal troughs. The encroachment took place parallel to the altered white matter, thus effecting a laminar pattern to the cortical changes. The lower layers, namely 5 and 6, were usually the first or exclusively affected. In sulcal troughs, layer 4 was also often involved. Here, the upper layers of the cortex showed only mild diffuse neuronal loss, accompanied by a marginal gliosis in the molecular layer.

C. Severe. A further extension of pattern B resulted in destruction of the entire width of the cortex in addition to the involvement in the underlying subcortical white matter (figures 2B and E). Since this occurred most commonly in the troughs of sulci, tapering off toward the crests, in this lesion a "U" type of pattern resulted. In the troughs the entire width of the cortex was affected. This diminished in the sides of the sulci to become progressively more subcortical until only the central cores of the white matter of the crests were involved, whereas the grey matter of the crests remained entirely intact. In effect, this resulted in a characteristic mushroom appearance to the gyri in these most destroyed zones. In these areas of "U" effect, the underlying white matter was most intensely involved and tended to show cystic change. Here, the "calcifications" were in the form of foci, either as plaques or minute granules.

Although nowhere in these severe sulcal lesions was there evidence of either occlusion or change in vessels, in "transition zones," regions at the sides of sulci where the severe effects tapered off into normal cortex, the lesions suggested a perivenous origin (figure 2B). Here, short radial centrifugal scars extended from the white matter for varying distances into the cortex, or extended through the entire cortical width. Between these scars, relatively intact clusters of cortex could be found. In a few instances, a venule from the overlying meningeal network could be traced into the white matter through one of these scars, although the vein always remained patent.

Thalamic lesions. These lesions differed from the cortical white matter changes in being more discrete and focal in nature and were separated by normal areas (figure 2C). At times, however, they tended to become confluent. Histologically, the lesions were less fibrous, containing relatively more astrocytic cells. The calcific deposits found within these scars varied from large dense plaques (figure 2F) to scattered encrusted neurons.

"Calcifications"

One of the unusual features of this chronic form of western equine encephalitis, as evidenced in our case, appeared to be the extent of deposition of basophilic material, commonly referred to as "calcifications," in the tissues affected by the disease. These deposits occurred in three forms: 1) as dense linear streaks or large isolated plaques (measuring 100_{μ} to 800_{μ}) (figures 2F and 3A), 2) as scattered minute foci in the scarred areas, and 3) as encrusted neurons.

On staining with hematoxylin and eosin or by the Nissl method, these basophilic deposits appeared dark blue and possessed distinct morphologic characteristics. They occurred in round circumscribed foci (*spheroids*) of 10 to 15_{μ} comparable in size to macrophages (figure 3D). They were made up of minute spherules (of 1 to 2_{μ} size), giving a grape-cluster appearance to them. Frequently, the spherules fused into a single large globular form. These deposits were not related to the vascular bed.

Various staining methods were used to give information as to the chemical nature of these basophilic deposits. Demineralization, achieved by placing deparaffinized sections in 10 per cent hydrochloric acid for 90 minutes, failed to alter the characteristic morphology or color observed in stains with hematoxylin and eosin. This would indicate that the underlying and essential nature of these deposits was organic. However, the von Kossa technic proved that calcium was a variable component of these deposits. Thus, calcium salts were found to be present in the deposits in the thalamus, but were in only sparse amount in the deposits in the cortical white matter lesions. This was so, despite the fact that deposits were of identical appearance in either site when stained with hematoxylin and eosin.

While basophilic deposits or "calcifications" in destructive brain lesions are found in cases of varying etiology, the extent and morphology of these in our case of western equine encephalitis suggested the presence of more specific pathogenic factors. In this regard, it would appear that the dense solid foci or globules (figure 3D-X) primarily represented fused and older-aged forms of the multinucleolated grape-cluster spheroid forms (figure 3D-Y). These latter forms, in turn, could be interpreted as the remains of phagocytes, filled with a unique, now altered and basophilic, organic debris, ingested during the acute destructive phase of the western equine encephalitis viral infection. In some instances, as in the thalamus, there finally occurred an encrustation of calcium salts upon this organic debris. Added evidence that these basophilic substances may be particularly associated with the viruses of the arthropod-borne encephali-

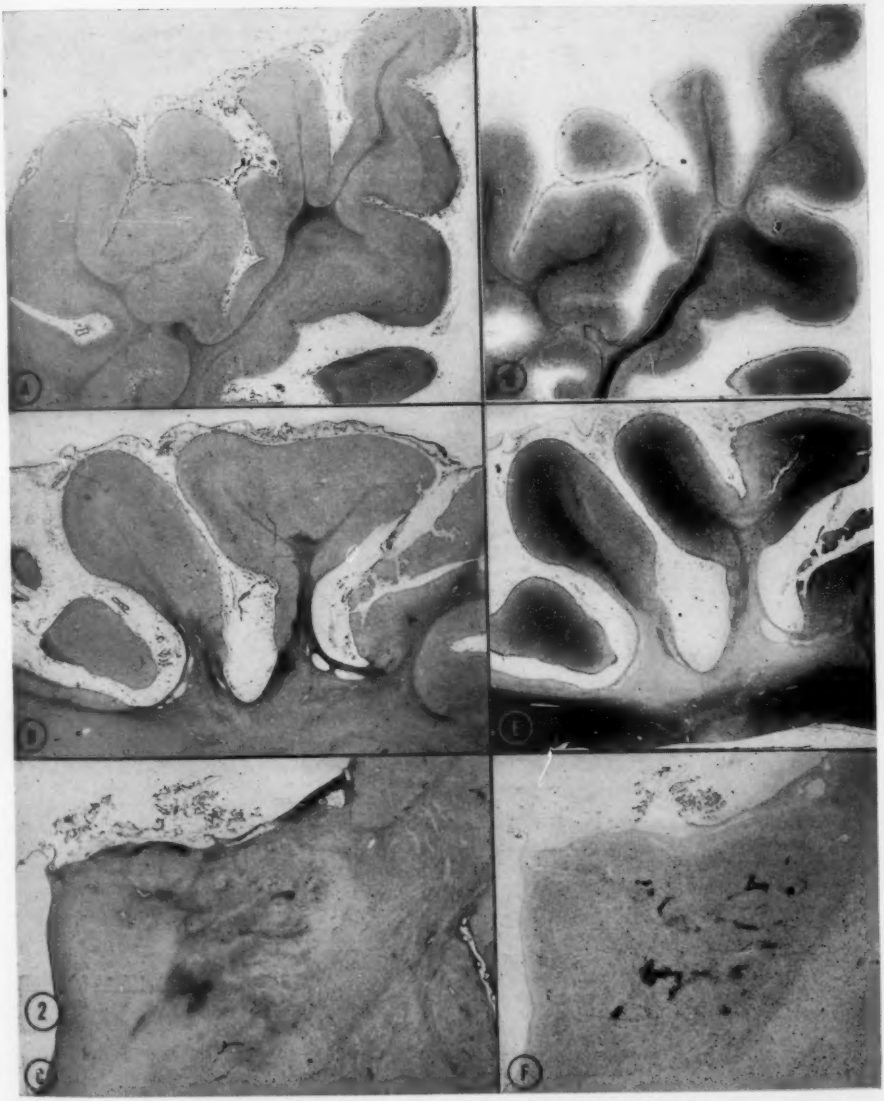

FIG. 2. *A, D.* Dorsal half of right frontal lobe, corresponding to figure 1A, showing mild pattern of atrophy affecting subcortical white matter, as gliosis in *A* (Holzer stain) and as demyelinization in *D* (Weil stain). *B, E.* Right frontal lobe, corresponding to dorsolateral area in figure 1B. Note "U" pattern of severe atrophy affecting cortex and subcortical white matter of troughs of sulci, thence extending into white matter core of gyral crests. Result is the formation of mushroom-like caps of retained cortex in the preserved gyral summits. *B,* Holzer stain; *E,* Weil stain. *C.* Thalamus, showing disseminated glial scars. Holzer stain. *F.* Same, calcifications occurring as focal plaques within the scars. Nissl stain.

tides may be gained from the report of Zimmerman,[35] who found "calcifications" in three subacute cases of Japanese B encephalitis.

"Active" Lesions

An unexpected finding was the presence in this case of glial nodes and perivascular lymphocytic "cuffing" (figure 3B and C). This was viewed as evidence of renewed or continued "activity."

The glial nodes occurred almost exclusively where the previously outlined scars were found. They were most numerous in the white matter and in the cortex, averaging four to five lesions per microscopic section, with lesser numbers in the thalamus. There were also occasional nodules in the putamen. The tegmentum of the midbrain was the only site in which a glial node was found unassociated with chronic lesions. One node was found here. It was noteworthy that nodes were not found in any other part of the brainstem, nor in the cerebellum and cervical cord.

The glial nodule was formed by microglia, varying from rod-shaped cells with vesicular nuclei to smaller irregular forms with pyknotic nuclei. Occasional nodules showed necrotic centers.

In distribution, the glial nodules were found equally in subcortical white matter and in cortex. In the latter, they were only found in the fifth and sixth layers, particularly in the sixth (figure 3B). Otherwise, these cortical layers were completely intact. These nodules always overlay gliotic white matter. "Calcifications" were frequently present in these designated white matter scars (figure 3B), but not necessarily so. In the white matter the nodules were all located immediately subcortical. They tended to be more frequent in areas that were only mildly to moderately involved, being less common in severely destroyed regions. Here, too, the nodules were found both adjacent to basophilic deposits or independent of them.

Perivascular cuffing with lymphocytes were present in lesser number than the microglial nodules. They predominated in the thalamus. They were less frequent in the cortex and white matter, and were not observed in the basal ganglia, the brainstem, cervical cord, or cerebellum.

Other Findings

A diffuse microgliosis in the form of rod cells was conspicuous throughout the central nervous system (figure 4). This was most pronounced in the cortex, where it was found equally in chronically affected areas as in intact parts of the grey matter. The thalamus and the subcortical and central white matter also contained diffuse rod cells, though in lesser numbers. Here, too, their presence was independent of the chronic lesions. Only mild infiltration with microglia was noted in the basal ganglia, and there was none in the brainstem or in the cerebellum. A number of Alzheimer glia were also dispersed throughout the cortex. In view of the terminal clinical course of the patient, we hesitate to positively link this diffuse microglial infiltration to the other signs of encephalitic activity in the brain, since the presence of these rod cells might also be interpreted as evidence of a "toxic" encephalopathy.

As has been previously stated, no occlusive phenomena were found in cerebral vessels. However, a mild proliferation of the endothelium of cerebral vessels was frequent, but this did not appear to be related to the areas of predilection of the chronic lesions. Amorphous basophilic material was present in a few of the small arteries of the putamen and the meninges overlying the cortex. This was deposited in the media and did not encroach on the lumen of these vessels. The deposits did not stain for calcium but did for iron. Nonetheless, their basophilic affinity could be demonstrated even after demineralization of the sections. These findings compare with those reported recently by Slager and Wagner[36] in a survey of basophilic deposits found in vessels of the basal ganglia in routine autopsy material.

A search for intranuclear or intracytoplasmic inclusions failed. Also, neurofibrillary changes of Alzheimer, seen in neurons in other forms of encephalitis, were not found here.

A bilateral sclerosis of Ammon's horn that affected the end plate stem and the nonresistant part of Sommer's sector was present. This was consistent with the epileptic history in this case.

DISCUSSION

Heretofore, reports of the pathology associated with sequelae of encephalitis have been concerned chiefly with those following attacks of the lethargic encephalitis of von Economo. The residua of the latter disease are primarily characterized by loss of neurons and replacement gliosis, limited to the substantia nigra and periaqueductal nuclei. There is insufficient information on the sequelae of the three North American arthropod-borne encephalitides, namely St. Louis encephalitis, eastern equine encephalitis, and western equine encephalitis. In view of a different pattern and distribution of the lesions in our case, it appeared to us important to compare the lesions in the various forms of these encephalitides, both in their acute and chronic stages.

Pathology of the Acute Stage

A survey of the literature concerned with the pathology in the acute stages of epidemic encephalitis of either A or B groups reveals that certain features appear to be common to all of these infections. These may be grouped under two types of inflammatory response, a) hematogenous, and b) glial.

The hematogenous response consists of a leptomeningitis and perivascular cuffing within the nervous tissue. In either case, the reaction consists primarily of lymphocytes, with smaller numbers of plasma cells and histiocytes. In the earliest stages, a polymorphonuclear neu-

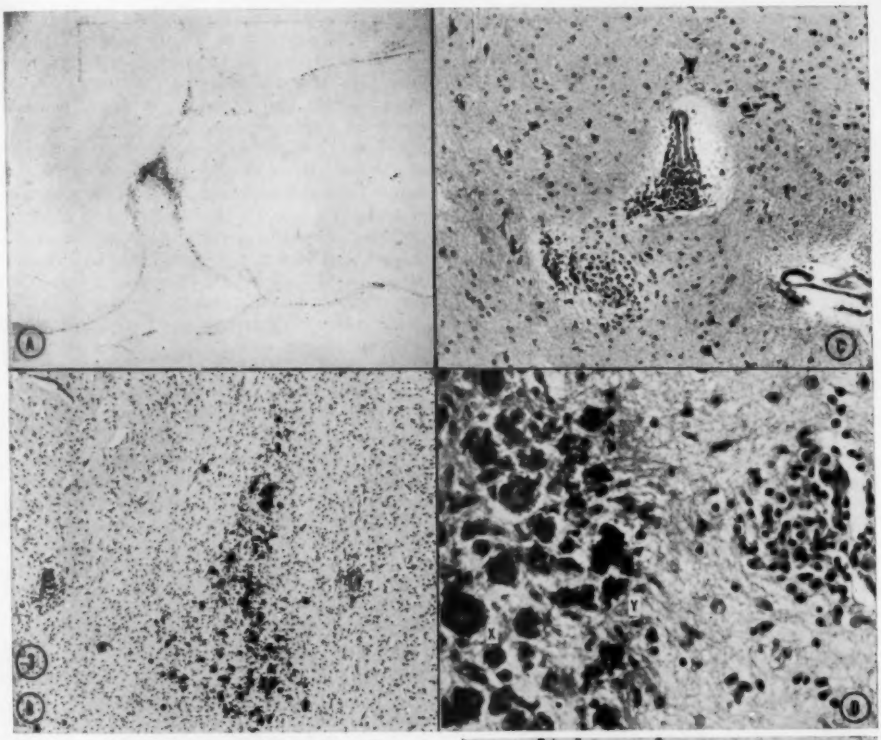

FIG. 3. *A.* Through an area of gliotic white matter in figure 2A, showing subcortical "calcifications" occurring as linear streaks and large plaques. Nissle stain. *B.* Two microglial nodes in lower cortical layers, with foci of "calcification" forming a plaque in subcortical white matter. Nissl stain. *C.* A microglial node with nearby locus of perivascular cuffing with lymphocytes, in thalamus. Nissl stain. *D.* Detail of "calcifications" in a plaque in subcortical white matter. At *Y*, "grape-cluster" form composed of multiple minute foci. At *X*, fused dense globule form. A microglial node to the right. Hematoxylin and eosin stain.

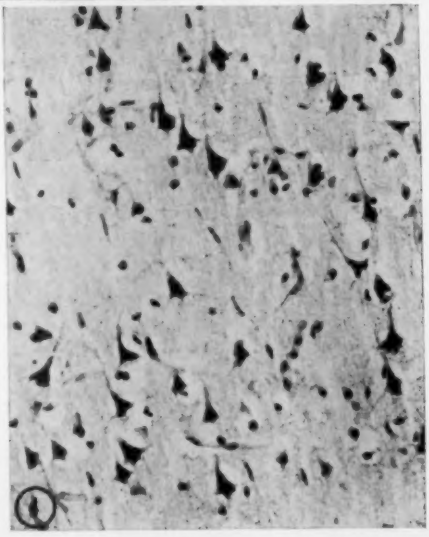

FIG. 4. Diffuse microgliosis in intact cortex. Nissl stain.

trophilic response may temporarily precede this mononuclear picture.

The glial reaction to the virus manifests itself in the development of foci of proliferation or "glial nodes." These foci accumulate either about neurons in the form of neuronophagia or in intercellular tissue. They are frequently associated with a more diffuse glial proliferation. The cellular constituent of this reaction is the microglial cell. Neurons in the immediate vicinity of either the glial or hematogenous reaction undergo alteration varying from mild to severe degenerative changes, accompanied by variable astrocytic proliferation.

Neurons at a distance are singularly unchanged.

Although the above changes occur as a common background for all these infections, it is evident that epidemics, the result of the different viruses, produce sufficient variation in pattern and distribution of the pathologic findings as to consider them of differential diagnostic value.

Lethargic encephalitis. Ayer[37] recorded the pathology in 50 cases of lethargic encephalitis during the epidemics of 1917 to 1920. Although this series comprised cases from both the European and the American epidemics, they were homogeneous pathologically. The particular predilection for the midbrain and the cranial nerve nuclei was striking. Less severe changes were noted in the basal ganglia and in the remaining areas of the pons and medulla, with only minimal involvement of the cerebral cortex, white matter, and spinal cord.

St. Louis encephalitis. Studies conducted following the St. Louis epidemic of 1933[38,39] and the smaller Ohio epidemic of 1934[40] have formed the basis for the neuropathologic findings in this disease. All writers were in agreement that the cerebral cortex and the white matter were generally more affected than in lethargic encephalitis. In addition, emphasis had been placed on the widespread involvement of the brainstem, in contrast to a predilection merely for the dorsal areas and cranial nuclei in lethargic encephalitis.[40] These distinguishing features were particularly striking in the severe cases, while the pathology in the milder cases more closely resembled that seen in von Economo's disease.

Eastern equine encephalitis. Wesselhoeft and co-workers[41] and Farber and co-workers[42] investigated the 1938 Massachusetts epidemic of eastern equine encephalitis. Dent[43] has reported his neuropathologic studies from the smaller 1947 Louisiana epidemic. Findings common to most of the cases in these reports were the predominant polymorphonuclear leukocytic infiltration both in the parenchyma and about the vessels, the relatively severe vascular infiltrations and endothelial proliferation, and the degree of cortical involvement, the latter approaching or equalling that observed in the brainstem. Two of the reports[41,43] emphasized the presence of focal and confluent areas of necrosis in this disease, most prominent in the lower cortical layers but also found in the central white matter, the basal ganglia, and the brainstem.

Western equine encephalitis. Five papers have been devoted to the histologic analysis of the acute case of western equine encephalitis. That the pathology in western cases can be similar to that found in St. Louis cases is apparent in the reports of Weil[44] and of Finley,[45] each of whom had the opportunity to study both types of cases. Weil found that a single differentiating feature in western equine encephalitis was the presence of focal necrosis and demyelinization, particularly in the white matter, but also in the cortex and in the striatum. Other authors[46–48] have also noted these necrotic foci in their cases.

Vascular changes have also been reported in western equine encephalitis. Baker and Noran[48] noted the prominence of severe swelling and proliferation of endothelium, frequently of such degree as to occlude the vessels. In a later report[51] these authors concluded that the primary effect of the virus of western equine encephalitis was on the cerebral vessels and that the areas of demyelinization observed were the direct result of partial obstruction of these vessels. Weil[44] noted endothelial swelling in his cases, but found no evidence of thrombotic phenomena. He concluded that the necrotic foci were unrelated to the vascular change, but instead had their origin in microglial nodes undergoing necrosis.

Pathology of the Subacute Stage

As examples of a possible transition state between the pathology in the acute and chronic forms of encephalitis, the following cases are included.

Quong[47] in 1942 described the case of a nine year old boy who survived a presumed attack of western equine encephalitis for 43 days. The diagnosis was made on the basis of the clinical picture in the presence of a single positive complement-fixation test. Clinically, the patient manifested persistent somnolence and signs of parkinsonism. Pathologically, there were isolated and confluent foci of softening, within which there was severe microglial proliferation. The lesions were most numerous in the substantia nigra, red nucleus, thalamus, and basal ganglia, with fewer lesions in the pons, medulla, and cerebral cortex.

Dent[43] recorded a case in a seven month old infant, presumed to be one of eastern equine encephalitic infection on the basis of a single serologic study revealing the presence of neutralizing but the absence of complement-fixing antibodies. The child survived for 53 days after onset of the illness and evidenced rigidity of the extremities, fever, and convulsions

throughout the duration of the illness. The brain showed widespread minute foci of cystic encephalomalacia, which were filled with gitter cells and macrophages. They were present in the cortex at the junction of the white matter, in the thalamus and basal ganglia, with only scattered lesions in the midbrain.

While both the case of Quong and of Dent had become ill during proved epidemics of equine encephalitis, unfortunately the serologic criteria for establishing either of these individual cases as proved instead of presumptive were not satisfied. Thus, we cannot be certain that the pathologic description in either of these cases can be considered as representative of the particular form of encephalitis.

Of interest is the report by Zimmerman[35] of three subacute cases (37, 48, 52 days) that occurred in the course of an epidemic of Japanese B encephalitis in Okinawa in 1945. This author found small cyst-like lesions confined to the grey matter of the cortex and the basal ganglia. Within these lesions, there was extensive deposition of calcium salts.

Pathology of the Chronic Stage

The chronic stages of lethargic encephalitis are too well known to warrant detailed discussion here other than to emphasize the restriction of the lesions to the substantia nigra and the periaqueductal nuclei. We have not been able to find reports concerned with the pathology of the chronic stages of either St. Louis or eastern equine encephalitis.

Noran and Baker have published three reports[49–51] dealing with the chronic lesions in western equine encephalitis. While serologic evidence was not offered to substantiate the diagnosis in their second[50] or third[51] cases, the authors concluded that the pathology in these two cases was sufficiently similar to their first case to be diagnostic. However, in their first case[49] only a single convalescent serum was studied for neutralization antibodies six months after the initial acute infection and a demonstration of a rise in titer was not possible. Since this case was suspicious of western equine encephalitis, it is reviewed here.

The case, that of a three and a half year old boy, was reported clinically by Platou.[14] The illness occurred at the age of four weeks during the course of a 1938 epizootic among horses in Minnesota. It was characterized by fever and frequent convulsions, though the infant recovered within ten days. There were no laboratory studies performed during the acute phase of the illness. At two months convulsions recurred, and thereafter the infant developed generalized spasticity. At the age of seven months a serologic test was first made and a high titer of neutralization antibodies against western equine encephalitis demonstrated.

In this case the grey and white matter, particularly in the frontal lobe, was severely destroyed, resulting in multiple glia-lined cavities. In some areas the white matter appeared to be more involved than the grey, and in a few foci, relatively intact upper cortical layers overlay the altered white matter. In scattered regions of the cortex a slight proliferation of microglia in the form of rod cells was present. The small vessels in the affected zones showed proliferation of the lining endothelium and their walls were frequently thickened and hyalinized. Thrombus formation was never observed, but calcium deposits were present in the walls of some vessels, occasionally replacing the entire vessel. There were also scattered calcium granules lying free in the parenchyma.

A second suspicious case of western equine encephalitis was reported by Bruyn and Lennette.[15] The patient, while residing in the Central Valley of California, developed an acute infection with high fever and convulsions at the age of eight months. Recovery was incomplete and was followed by mental retardation, generalized rigidity, and convulsions. Two months after the onset of the illness serologic tests were first performed, revealing a non-elevated complement-fixation titer but a high neutralization titer to the virus of western equine encephalitis. While these studies were not conclusive, the authors considered it reasonable to relate the high antibody titer to the child's illness. Nonetheless, in our opinion, the requirements for a positive serologic diagnosis were never satisfied. Death occurred at three years of age.

In the brief description of the pathology in this case, it was noted that pale, sclerotic areas of 1 to 2 cm. diameter were present in both basal ganglia, in the subcortical white matter of the left parietal lobe, and in the right temporal lobe. Microscopically, there were disseminated foci of gliosis throughout the cerebrum. Focal accumulations of calcium and macrophages were observed in some areas, while in others, a perivascular lymphocytic reaction was present.

PATHOGENESIS

A comparison of the distribution of the lesions in our chronic case with those recorded

in acute cases offers us some leads in interpreting certain elements bearing on the pathogenesis of the sequelae of western equine encephalitis.

For the acute stage of western equine encephalitis, the distribution of the inflammatory foci, comprising glial nodes and perivascular cuffing, can be formulated from a review of the five reports above.[44–48] The greatest numbers of such foci were found in the midbrain, moderate numbers in the striatum and thalamus, lesser numbers in the cerebral white matter and pons, while few elements were present in the cerebral cortex, medulla, cervical cord, and cerebellum. The chronic lesions in our own case do not reflect this distribution, since they were most numerous in the cerebral white matter, cortex, and thalamus, and were entirely absent in the brainstem. Therefore, it would appear that the inflammatory foci in themselves do not lead to permanent damage. This finding is not as paradoxical as it would seem when certain other viral infections of the central nervous system are recalled. For example, in acute anterior poliomyelitis, involvement of the posterior horns, brainstem, and diencephalon is commonly observed, yet residual lesions are confined almost exclusively to the anterior horns. Similarly, the acute lesions in von Economo's disease, while most pronounced in the midbrain, are present also in other areas, such as the striatum, pons, and medulla. Nonetheless, chronic lesions in this disease are confined to the substantia nigra and to the periaqueductal nuclei.

It is our premise that the sequelae and chronic lesions of western equine encephalitis are directly related to the necrotic rather than to the inflammatory foci of this disease. To support such a hypothesis, the distribution of necrotic foci in western equine encephalitis was analyzed. While the distribution of these necrotic foci in the acute case was not described as adequately as was that of the inflammatory foci, it would appear, particularly from reports by Weil[44] and by Baker and Noran,[48] that necrotic foci were found predominantly in the white matter and to a lesser degree in the cortex and striatum, whereas the brainstem and spinal cord were not at all subject to such lesions. In our case, the chronic lesions were similarly restricted to the subcortical white matter, to the adjacent cortex by extension, and to the thalamus. In our opinion, therefore, the chronic lesions could more readily be considered as having resulted from the necrotic rather than from the inflammatory foci of the acute stage of the disease.

The essential origin of these necrotic foci has been a subject for debate. While some authors[49,51] regarded these to be of vascular obstructive etiology, others[44,45] considered that necrotic areas develop within microglia nests. We would further interpret this necrotic tendency as evidence of such high virulence of the virus that the very defense mechanism against the virus is itself overcome and destroyed. This propensity for increased virulence and associated necrotic lesions appears to be common to many of the viruses of the B group of encephalitides.

Still another mechanism for the production of the type of lesions in our case suggests itself. Rather than discard the one just advanced, we wonder whether a second and vascular mechanism may have been superimposed on the first, that of a disturbance occurring in the territory of drainage of the external cerebral veins. This was assumed on the basis of: 1) the restriction of the lesions to the superficial and dorsolateral areas of the brain, 2) their predilection for the troughs of sulci, from which they extended in "U" fashion into the gyral white matter of the crests, and 3) the similarity of some of the lesions to so-called status marmoratus, a lesion commonly seen in cases of cerebral palsy resulting from birth injury. A venous role in the pathogenesis of the latter condition has also been considered.

The disturbance in the external cerebral venous system as postulated in our case would not take the form of a gross thrombosis, nor affect the larger meningeal vessels. It could probably result from involvement of the sulcal penetrating veins by a process of stasis or phlebitis, perhaps produced by necrotic foci lying within the subcortical white matter or cortex of the sulcal areas.

The presence of glial nodes and perivascular cuffing in our case would indicate either a mild acute new form of encephalitis or a persistence of the original western equine encephalitic infection. In favor of the latter condition would be the observation that these inflammatory foci were at all times located in the immediate vicinity of older lesions in the case and were not found widely spread throughout the brain. As evidence of a probable persistence of the viral infection in a dormant controlled equilibrium between parasite and host, these findings are unusual. While our case would be the first instance of a chronic form of encephalitis occurring in a proved case of infection with a virus of the North American

arthropod-borne encephalitides, similar evidence of a reactivated or smoldering infection in viral disease of the nervous system is known in von Economo's form of encephalitis and recently has also been reported in the inclusion form of encephalitis.[52]

SUMMARY

The case of a five year old boy, evidencing severe intellectual and mild neurologic sequelae following a serologically confirmed attack of western equine encephalitis at the age of one month, is reported clinically and pathologically. Extensive cerebral lesions were found, consisting of glial scars within which basophilic deposits were prominent. The lesions were largely confined to the subcortical white matter and to the thalamus. The cortex was also variously involved by encroachment of the white matter process, particularly in sulcal troughs where it produced a characteristic "U" pattern of destruction. There were no residual changes in the brainstem, cerebellum, or cervical cord. It is proposed that the lesions represented confluent necrotic foci developed during the acute stages of the infection. A unique finding was the presence of scattered microglial nodes and perivascular cuffing immediately adjacent to these scars. These inflammatory lesions were interpreted as evidence of still persistent viral activity. Pertinent literature is critically reviewed.

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■ Nor need the symptoms of common paraplegia (resulting from chronic myelitis) be confounded with those of locomotor ataxy. In common paraplegia there is paralysis more or less marked of the lower extremities, and the nutrition and irritability of the paralyzed muscles are, as a rule, unmistakably impaired; not so in locomotor ataxy. In common paraplegia the paralysis extends to the bladder and sphincter ani, and the sexual power is greatly weakened, if not altogether abolished; not so, or not to anything like the same degree, in locomotor ataxy. In common paraplegia the characteristic neuralgic pains of locomotor ataxy are wanting, and numbness is nothing like so prominent a symptom as in the ataxic disorder. In common paraplegia, where walking is possible, the gait—instead of being precipitate and staggering, the legs starting hither and thither in a very disorderly manner, and the heels coming down with a stamp at each step, as in locomotor ataxy—is hampered and slow, each leg being brought forward with evident difficulty, even with the help of an upward hitch of the body on the same side, and the part of the foot first coming in contact with the ground being, as a rule, not the heel, as in ataxy, but the toes.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

Paroxysmal Abdominal Pain as a Manifestation of Epilepsy

Joseph L. O'Brien, M.D. and Eli S. Goldensohn, M.D.

PAROXYSMAL ABDOMINAL PAIN as a form of epilepsy is a fairly well established clinical entity. Several groups of patients with this syndrome have been reported.[1–4] In 31 children studied by Hoefer and co-workers,[4] the pain was characteristically periumbilical or epigastric. It usually persisted from a few minutes to several hours. In most instances other gastrointestinal symptoms such as anorexia, nausea, vomiting, diarrhea, or constipation were present. Four had experienced convulsive phenomena prior to or concurrent with the onset of abdominal complaints, while six developed seizures in later years. Eight had generalized seizures and one had psychomotor seizures only. The electroencephalogram showed abnormally slow activity in the resting records of 28 cases and was "borderline normal" in one. Sixteen patients had rapid or spike activity, or both, and four had spike and wave bursts. There were no clear-cut focal signs. Thirty cases had an abnormal response to hyperventilation.

Moore[5] studied 28 patients with this syndrome. He stated that in approximately 50 per cent the cause of the abdominal pain was an organic cerebral lesion. In his own cases and in others which he reviewed 67 to 80 per cent had abnormal electroencephalograms.

Livingston[3] described 14 children with abdominal epilepsy. Three had pain lasting as long as 24 to 36 hours. Definite electroencephalographic abnormalities were noted in 11 cases, while three were considered to be normal. The abnormalities observed were as follows: four cases had excessively fast activity; four were excessively slow; one had paroxysmal bursts of spikes; one showed high voltage slow spike and wave forms; and one had a slow wave focus. In the case of the child with the slow wave focus between attacks, an electroencephalogram was also obtained during an attack of abdominal pain. High voltage 2 cps. activity in all leads occurred coincident with the onset of abdominal pain and persisted for the duration of the attack. The generalized high voltage slow activity ceased shortly after the pain was gone. To our knowledge, this is the only previously reported instance in which a tracing showed electroencephalographic changes directly correlated with the attack.

During the study of a patient with recurrent bouts of abdominal pain in whom the diagnosis of abdominal epilepsy was suspected, we had the opportunity to obtain an electroencephalogram while the patient was experiencing an attack. This is a second instance of the occurrence of reversible modification of the electroencephalogram during an episode of paroxysmal abdominal pain.

CASE SUMMARY

A nine year old girl had two admissions to Babies Hospital, the first from February 25 to March 10, 1956 and the second from April 28 to May 10, 1956. On each occasion the chief complaint was abdominal pain. The child had been well until the age of five, when she began to experience episodes of periumbilical pain with vomiting. These recurred at five to six week intervals and lasted about five days each. Usually loss of appetite and facial pallor preceded the attack by several days. The periumbilical pain was sharp, cramp-like, and paroxysmal. It occasionally awakened her from sleep. The pain was of sufficient severity to confine her to her home for the first day or two. Usually she was nauseated and vomited four to five times the first day and once or twice the second day. This was followed by nausea for three days, with gradual return of appetite.

Birth and early development were not remarkable, except for the fact that she was a poor eater and tended to vomit easily. At five months of age she was admitted to another hospital because of an episode of vomiting. Until the age of five she continued to eat poorly, and forcing of food at mealtime by her mother caused vomiting. Although this difficulty disappeared at age five, she remained underweight until she was seven.

The child's parents were divorced when she was six. Since then she has lived with her mother and her ten year old sister. The mother had a "nervous breakdown" in 1948.

At the time of her first admission, the patient complained of abdominal pain associated with fever of three days duration. For the first two days vomiting had been present. Examination on February 25, 1956 disclosed a well developed and well nourished child complaining of severe abdominal pain. Temperature was 100.6° F., pulse 92,

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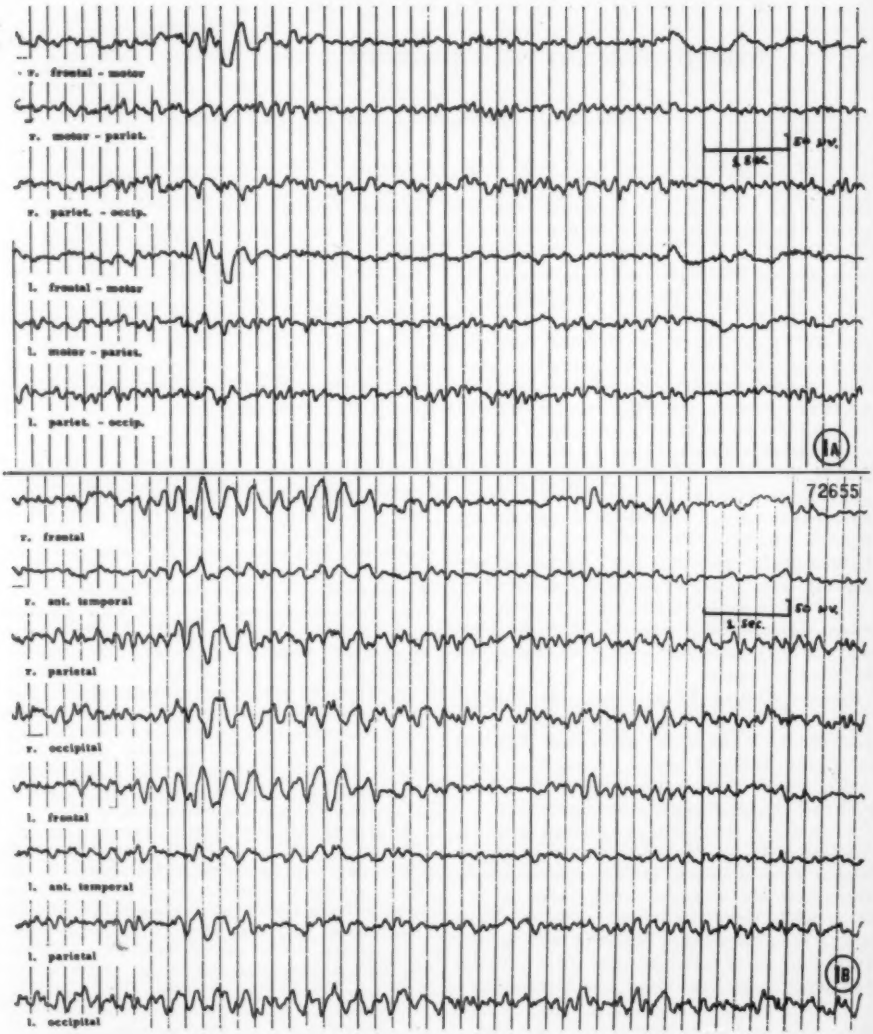

FIG. 1. Electroencephalogram of March 7, 1956. Patient asymptomatic. *A*, resting. *B*, at three minutes of hyperventilation. Calibration, timing, and electrode placement are as shown in the illustration.

and respirations 16. Except for some mild periumbilical tenderness, the general physical and neurologic examinations were unremarkable.

Laboratory examinations: On February 23 hemoglobin was 14.4 gm./100 ml. The white count was 21,000 per cu.mm., with 86 per cent polymorphonuclears, 10 per cent lymphocytes, 3 per cent monocytes, and 1 per cent eosinophils. On February 27 the white count was 11,800/cu.mm., with 69 per cent polymorphonuclears, 24 per cent lymphocytes, 6 per cent monocytes, and 1 per cent eosinophils. Urinalysis was unremarkable. Sedimentation rate was 50 mm./hour. Roentgenographic studies of the abdomen, hands, wrists, and knees were normal.

The abdominal pain disappeared the first day after admission. Mild fever persisted for two days. On the third day she developed a sore throat. He-

molytic streptococci were found on culture from the nasopharynx, and a course of penicillin was administered. She had no further abdominal complaints.

Ten days following admission the electroencephalogram taken on March 7, 1956 was interpreted as mildly abnormal because of some suggestive paroxysmal features (figure 1). In the resting record, a few medium voltage groups of 3 to 4 cps. waves were noted bifrontally. With hyperventilation 3 to 3½ cps. waves occurred in bursts lasting 1 to 2 seconds each. She was discharged on March 10, 1956.

On April 28, 1956 the child was readmitted because of recurrence of abdominal pain. She had been well following discharge until ten days before the second admission, when she again complained of anorexia and continuous mild abdominal pain. On the following day she vomited several times and the pain became more severe but intermittent. The general physical and neurologic findings were essentially the same as on the previous admission.

Laboratory examinations: Hemoglobin was 13.5 gm./100 ml. Leukocytes numbered 8,500/cu.mm. with a normal differential count. Urinalysis was unremarkable. Serum sodium 136.5 mEq./l.; blood calcium 11.0 mg./100 ml.; fasting blood sugar 61 mg./100 cc.; nonprotein nitrogen 39 mg./100 ml. Tuberculin test was negative. On lumbar puncture the initial pressure was 160 mm. of water. No cells were seen and the protein was 12 mg./100 ml. An intravenous pyelogram was negative. Examination of the stools for blood was negative. Barium enema and upper gastrointestinal series were normal, except for some prominent mucosal folds in the region of the duodenal bulb.

The abdominal pain disappeared on the second day of hospitalization. An electroencephalogram taken on the following day, April 30, 1956, was similar to the one recorded during the first admission but a little more disorganized. The child remained well until she was discharged on May 10, 1956.

A few weeks after leaving the hospital she had another episode of abdominal pain and was given phenobarbital 30 mg. three times daily which she took irregularly. In July she had another attack. On August 16 she came to the pediatric clinic because of pain of three days duration similar to those described previously. Her behavior was subdued and there was tenderness and spasm in the epigastrium. An electroencephalogram was recorded on the same day (figure 2). The pain was apparently of a mild degree during most of the recording time. The record consisted, for the most part, of runs of partly synchronous high voltage 3 cps. waves in all leads which were especially prominent in the frontal areas. There were no focal signs or asymmetries. At one period the pain became more severe. During this time there was an increase in both the number and in the synchrony of the 3 cps. waves (figure 2).

On the following day, August 17, while she was still experiencing some degree of pain, a gastrointestinal series was performed and interpreted as normal. Two days later, August 19, the patient no longer had abdominal complaints, but her mother felt that she was withdrawn and not yet her usual self. An electroencephalogram on that day still showed occasional bursts of 3 cps. high voltage waves, with large amounts of 4 to 6 cps. activity. With hyperventilation, large numbers of synchronous 3 cps. high voltage waves appeared. One month later, September 17, when the patient was asymptomatic, a follow-up electroencephalogram was taken (figure 3). This record was considered essentially the same as the other interim tracings.

Since discharge the patient has continued to suffer repeated bouts of abdominal pain despite attempts at control with anticonvulsants. Further electroencephalograms could not be obtained.

DISCUSSION

Several authors[2–4] have described abnormal cortical electrical activity between attacks of abdominal epilepsy. The present case and the one described by Livingston,[3] however, demonstrate electroencephalographic abnormalities recorded during the seizure itself. In both instances, the resting records were considered to demonstrate some degree of abnormality. In Livingston's case there was a slow wave focus in the left occipital region, while in the present case there were suggestive generalized paroxysmal features. In both cases, slow activity, frequently at high voltage and in the 2 to 3 cps. range, was dominant during the period of abdominal pain. This activity was both synchronous and generalized bilaterally. In Livingston's case, the pain and the slow activity persisted simultaneously for about ten minutes. In our patient, the abdominal complaints had already been present for four days before the electroencephalogram was taken. The day after pain had disappeared, the tracing was still significantly abnormal. However, the patient was subdued, quiet, and "not quite herself" at that time. The duration of continuous abdominal pain in this patient is longer than any previously reported case of abdominal epilepsy.

It was of interest that the synchronous paroxysmal activity was intensified when an exacerbation of pain occurred. It is possible that the prolonged period of cerebral dysrhythmia during pain is secondary to discharges originating in deep or midline structures and therefore cannot be correlated exactly with the paroxysmal pain either in time or intensity. In the intervals of four to six weeks between attacks, the tracing continued to be moderately to mildly abnormal, as is frequently noted between attacks in other types of convulsive disorders.

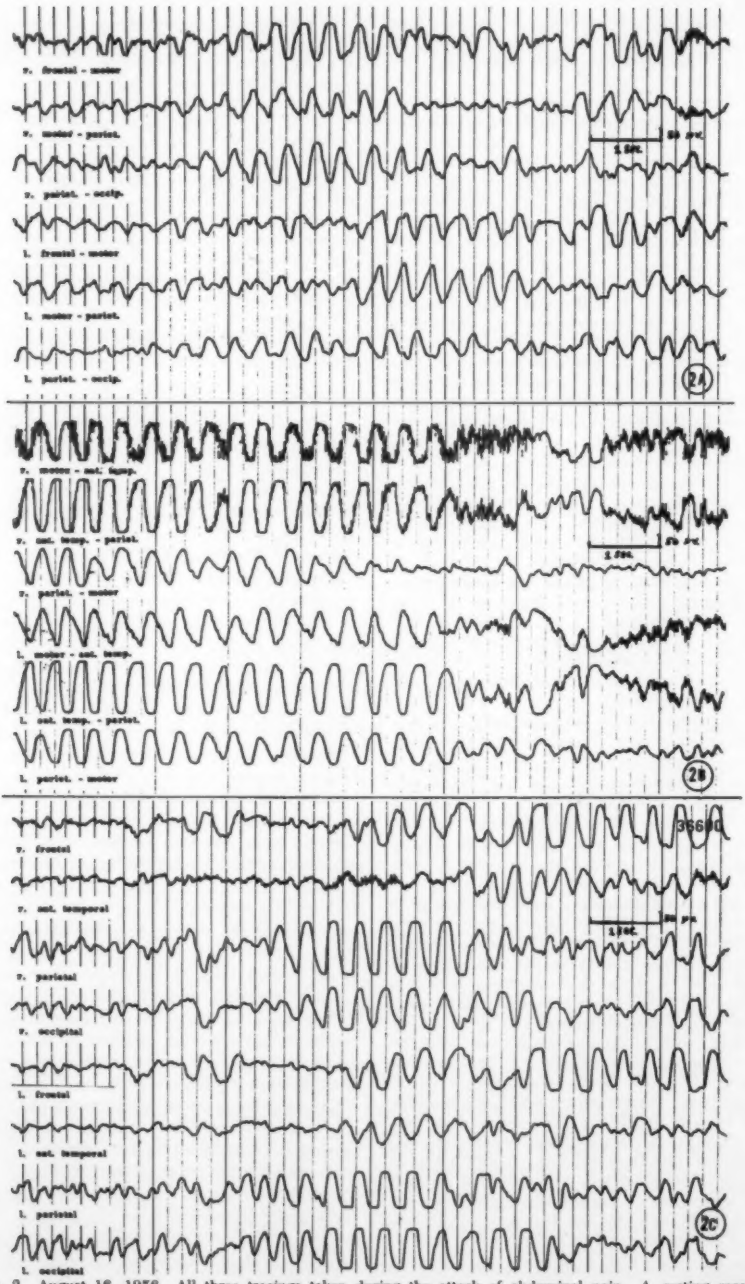

FIG. 2. August 16, 1936. All three tracings taken during the attack of abdominal pain. *A*, resting record. *B*, resting record during an exacerbation of pain. *C*, at two minutes and 40 seconds of hyperventilation.

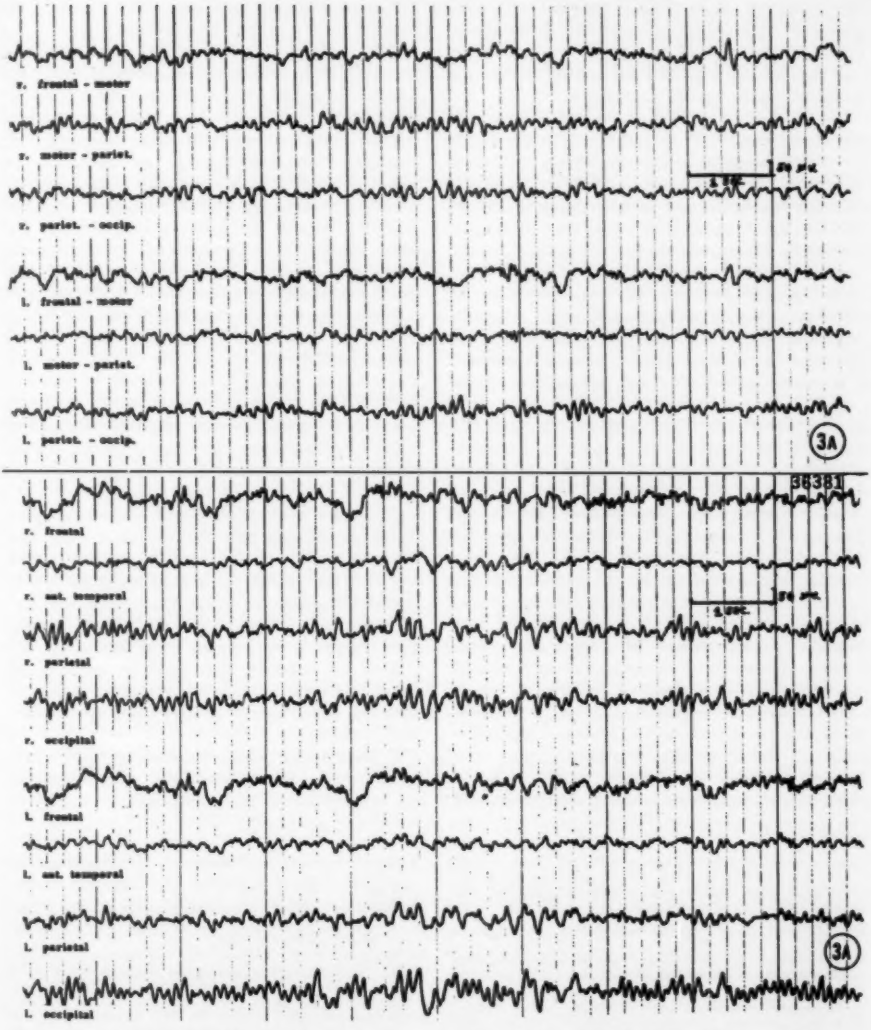

FIG. 3. September 17, 1956. Patient asymptomatic. *A*, resting record. *B*, at five minutes of hyperventilation.

The relationship of the central nervous system to intestinal motility has been demonstrated by many investigators. Beattie and Sheehan[6] and Wang and co-workers[7] have shown that hypothalamic stimulation may produce either increased or decreased motility of the gut. In 1854 Schiff[8] produced hypermotility of the intestinal tract by stimulation of the brainstem, and more recently Borison and Wang[9] have demonstrated a vomiting center in the medulla. Fulton and his co-workers,[10] as well as Spiegel and his associates,[11] have shown by stimulation and ablation experiments the effect of frontal area 6 and areas 5 and 3 of the parietal lobe upon gastrointestinal activity.

Increased and inhibited gastric motility has been reported in animals from stimulation of

the posterior orbital and anterior cingulate gyrus.[12,13] Retching has occurred from stimulation of the medial amygdala.[14] Borborygmi and flatus have followed stimulation of the anterior cingulate gyrus in man.[15]

Penfield and Faulk[16] have emphasized the effect of stimulation and ablation of the insula on gastric motility in human beings. Although their patients experienced abdominal sensation during stimulation, the authors were unable to say whether this sensation was actually represented in the insula or was secondary to the intestinal activity produced. It is difficult when studying this modality to know whether an effect is primarily sensory or whether it results from movement of the gut. A somewhat parallel situation exists in abdominal epilepsy where it is uncertain whether the perception of the pain is primary or whether it is the recognition of disordered intestinal activity. It may be that in those patients where pain is unaccompanied by other gastrointestinal symptoms, dysfunction of an area primarily involving sensation is in operation. On the other hand, when the episode is accompanied by vomiting, diarrhea, abdominal tenderness, and other signs pointing to the presence of intra-abdominal motor disturbances, the painful sensations may be secondary to abnormal intestinal motility caused by disturbance of autonomic motor centers. Hoefer and co-workers[4] described a 15 year old girl with abdominal epilepsy in whom a gastrointestinal roentgenographic study was made during paroxysms of pain. Three episodes of transient ileal intussusception were demonstrated. No abnormality could be found when the patient was without symptoms. In the present case, however, x-ray studies performed during pain were normal.

The pathology of the central nervous system in cases with abdominal epilepsy is as varied as that in other convulsive disorders. Moore[5] considered organic lesions such as cerebral trauma, brain tumor, tuberous sclerosis, and scarlatinal encephalopathy as causative in about one-half of his cases. In most other reports[3,4] the etiology of the condition was considered obscure. In most cases treatment has been mainly symptomatic. Anticonvulsant medications, such as phenobarbital or Dilantin, have usually been employed. Blumberg[17] recently reported the successful treatment of a case with Tridione after there was a poor response to Dilantin.

SUMMARY

1. Many authors have reported abdominal epilepsy in children who have periodic attacks of abdominal pain and electroencephalographic abnormalities between attacks.

2. A case is presented with electroencephalographic changes recorded before, during, and after an attack of abdominal pain. Between episodes the record contained suggestive paroxysmal features. During the attack the record consisted of runs of partly synchronous high voltage 3 cps. waves in all leads.

3. It is possible that pain is primary in some cases of abdominal epilepsy, while in others it is secondary to abnormal gastrointestinal motility.

4. In most instances the etiology is obscure. Symptomatic treatment with anticonvulsants has been reported to be effective.

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Disparity Between Low Cerebral Blood Flow and Clinical Signs of Cerebral Ischemia

Ralph W. Alman, M.D. and Joseph F. Fazekas, M.D.

PREVIOUS STUDIES[1,2] on the effects of acute hypotension upon cerebral circulation and metabolism have suggested that for each individual there is a critical rate of cerebral blood flow, below which functional or electroencephalographic abnormalities suddenly appear as evidence of central nervous system ischemia. This "critical rate" of cerebral blood flow in the above studies appeared to be approximately 30 to 35 cc. of blood per 100 gm. of brain per minute. Nevertheless, the occasional observation of individuals (usually elderly) having rates of cerebral blood flow even less than the above values with apparently normal brain function suggested that the "critical level" of reduced cerebral blood flow might actually be more accurately a "critical proportion" of the habitual flow. The present investigation was instituted to determine whether this were indeed the case or whether in such individuals the rate of cerebral blood flow is very close to the "critical level."

METHOD

The data from 700 observations on quantitative cerebral hemodynamics and metabolism were reviewed and cases were abstracted in which mentally alert subjects had been found to have cerebral blood flow values in the neighborhood of or below previously estimated average critical values. Observations were discarded in which certain extraneous factors, such as hypotension, polycythemia, and so on, might have complicated the interpretation of the results. There remained 34 subjects who were well oriented and responded appropriately to questions regarding time, place, and person. There was no evidence of hallucinosis or delusions in any of these individuals. Intellectual capacity, however, was not examined and there may well have been defects in this sphere. In any case, this information would have been of little value unless compared with the subjects' intellectual status in the prime of life.

In 14 of these cases, additional observations were subsequently made in the presence of induced hypotension, the arterial blood pressure being reduced by means of the intravenous administration of ganglionic blocking agents (Arfonad or hexamethonium) and then further altered by positioning the patient. In all except three of these 14 cases, estimation of cerebral blood flow was based upon cerebral arteriovenous oxygen differences during hypotension, assuming the cerebral oxygen consumption determined in the control state to remain constant. Previous studies[1] have indicated that this assumption is valid. In the three exceptions noted, the same method of study was used in the hypotensive as in the control phase.

Control studies in all subjects were made using Scheinberg's modification[3] of the Kety and Schmidt procedure[4] for the determination of cerebral blood flow. The gas mixtures utilized were those described by Kety and Schmidt.[4] The oxygen content of the blood was determined by the manometric technic of Van Slyke and Neill.[5] Mean arterial pressure (MAP) was obtained directly from the femoral artery by means of a damped aneroid manometer.[6]

RESULTS

Table 1 presents values obtained in 20 subjects ranging in age from 35 to 87 years, in whom low levels for cerebral blood flow had been obtained in the absence of hypotensive blood pressure levels. The mean age of these subjects was 62 years. Total cerebral blood flow varied from 23.6 to 31.9 cc. of blood per 100 gm. of brain per minute, the mean value being 28. Cerebral oxygen consumption ranged from 1.0 to 3.2 cc. of oxygen per 100 gm. of brain per minute, the mean value being 1.9. The cerebral vascular resistance was unusually high (mean value 4.3 units), related to the presence of hypertension and/or cerebral atherosclerosis in almost all of these subjects. Mean arterial blood pressure, although variable, showed an average value of 119 mm. Hg.

Table 2 presents the results of studies of 14 patients in whom, following control studies,

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TABLE 1
SUBJECTS HAVING LOW CEREBRAL BLOOD FLOW AND SATISFACTORY CEREBRAL FUNCTION

Subject	*Age*	*CBF*	*$CMRO_2$*	*CVR*	*MAP*	*Diagnosis*
E. B.	53	26.1	2.6	5.4	140	CVA
C. R.	55	24.7	1.5	6.5	161	CVA
W. D.	77	27.8	1.4	4.0	112	Congestive failure
A. P.	67	25.7	1.0	5.8	150	CVA
L. S.	56	30.2	2.4	4.9	147	CVA
R. W.	54	31.3	1.5	2.8	89	Diabetes
W. S.	79	25.3	2.1	3.1	78	CVA
R. J.	79	26.4	1.2	4.6	120	CVA
B. F.	60	29.8	1.1	4.7	140	CVA
S. W.	52	26.8	3.1	4.8	130	CVA
L. K.	73	30.4	2.1	3.4	102	CVA
A. H.	56	31.9	1.6	3.1	100	Diabetes
N. B.	65	23.6	1.3	5.2	122	CVA
M. C.	47	29.2	1.7	3.9	114	CVA
C. B.	87	30.0	3.2	3.4	102	ASHD
S. G.	62	27.7	1.6	3.6	100	Vertigo
W. S.	51	30.4	2.8	4.9	149	Malignant hypertension
J. K.	35	30.2	2.1	2.8	85	Alcoholism
H. D.	85	27.8	2.0	2.8	78	HCVD
E. P.	53	26.3	1.5	5.9	154	Hypertension
MEAN VALUES						
	62	28.1	1.9	4.3	119	

CBF, cerebral blood flow in cc./100 gm. of brain/min.; $CMRO_2$, cerebral oxygen consumption in cc./100 gm. of brain/min.; CVR, cerebral vascular resistance in mm. Hg/cc. blood/100 gm. of brain/min.; MAP, mean arterial blood pressure in mm. of Hg.

hypotension was induced by the administration of a ganglionic blocking agent (Arfonad or hexamethonium). In most of these subjects, the additional effect of changes in body position on cerebral blood flow was also investigated. In every case the administration of the hypotensive drug significantly reduced the blood pressure, with an attendant fall in cerebral blood flow. The degree of reduction in cerebral blood flow in most instances could not be correlated with severity of signs and symptoms of cerebral ischemia. In some cases marked symptoms were observed to attend a relatively slight reduction in cerebral blood flow; in others, a profound fall in cerebral blood flow was accompanied by relatively slight symptomatology, and in still others the development or amelioration of symptoms, induced by tilting the patient, were accompanied by changes in cerebral blood flow in a direction opposite to that anticipated. Possibly in not a few of these cases the changes noted were not significant and might be attributed to inaccuracies of the method employed.

Figure 1 illustrates the poor correlation between degree of fall in cerebral blood flow and appearance of symptoms of cerebral ischemia. These symptoms were graded as mild (nausea, yawning, anxiety, lethargy), moderate (semistupor), or severe (convulsions or unconsciousness). It is noteworthy that moderate symptomatology was observed only twice. Probably this can be attributed to the rapidity of transition between mild and severe cerebral ischemia, if hypotension and reduced cerebral blood flow were not immediately corrected.

DISCUSSION

The results of the present study indicate that an individual having a total cerebral blood flow

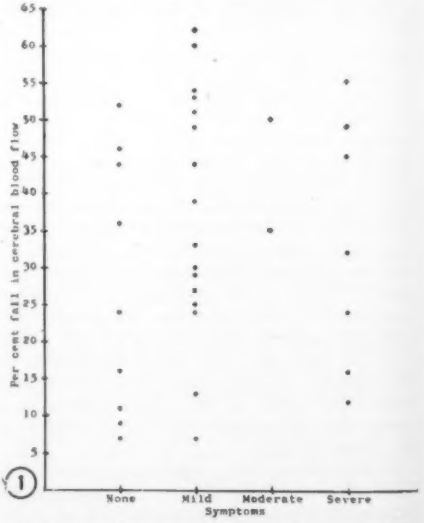

FIG. 1. Correlation between degree of fall in cerebral blood flow and appearance of symptoms of cerebral ischemia.

of less than 35 cc. of blood per 100 gm. of brain per minute may nevertheless remain alert and possess apparently satisfactory cerebral function. In some of these individuals it is possible to reduce the cerebral blood flow further to remarkably low levels without producing apparent impairment of cerebral activity; in others of this group, there is relatively little tolerance to further reduction of total cerebral blood flow. In contrast to the above observations, cerebral functional deterioration of senile individuals may sometimes be observed in the presence of relatively normal rates of cerebral blood flow and metabolism. The disagreement in correlation between clinical findings and rates of cerebral blood flow or tolerance to further reduction of these rates is worthy of speculation.

In most of the elderly subjects of the present study, there was a demonstrable and often marked reduction in cerebral oxygen utilization. In some cases, this factor may have permitted a considerable reduction in an already low rate of cerebral oxygen delivery without the appearance of cerebral ischemia symptoms. That this was probably not the most important element of cerebral metabolic-circulatory homeostasis is indicated by the observation that, as a protective mechanism, it failed in a considerable number of our subjects.

The abruptness of appearance of clinical evidence of cerebral ischemia in this, as well as

TABLE 2

EFFECTS OF ACUTE HYPOTENSION WITH TILTING ON SUBJECTS HAVING HABITUALLY LOW RATES OF CEREBRAL BLOOD FLOW

		Control				Hypotension						
Case	*Age*	*CBF*	*AVO_2*	*MAP*	*$CMRO_2$*	*CBF*	*AVO_2*	*MAP*	*Tilt*	*Drug*	*Pct. Fall CBF*	*Symptoms during Hypotension*
1	60	34.2	7.65	127	2.6	23.9	10.88	58	0°, 8 min.	Arfonad	30	Withdrawn
						30.1	8.65	62	—10°, 2½ min.		12	Unresponsive
						23.4	11.10	94	—10°, 8 min.		32	Unresponsive
						28.6	9.08	110	0°, ½ min.		16	Normal
2	59	24.6	9.89	170	2.4	23.0	10.43	97	+10°, 2¼ min.	Hexameth.	7	Normal
						23.0	10.44	76	+10°, 3 min.		7	Yawning
						18.8	12.79	53	+10°, 3¾ min.		24	Convulsion, cyanosis
3	69	26.1	3.80	98	1.0	12.3	8.12	40	0°, 1 min.	Arfonad	53	Lethargic but in good contact
						10.5	9.57	35	0°, 2½ min.		60	" " "
						11.9	8.42	40	—10°, ¾ min.		54	" " "
						18.9	5.28	33	0°, 1 min.		27	" " "
						14.6	6.84	34	0°, 2¾ min.		44	" " "
4	54	36.4	5.59	216	2.0	19.7	8.55	65	+18°, 4 min.	Arfonad	46	Normal
						17.3	10.18	60	+18°, 7 min.		52	Normal
						23.4	8.57	81	0°, ¼ min.		36	Normal
5	65+	35.3	4.61	154	1.6	19.2	8.32	76	0°, 3¾ min.	Arfonad	46	Normal
						17.5	9.15	123	—17°, ¾ min.		50	Moaning
						16.0	10.08	36	+20°, 3 min.		55	Unconscious
6	79	36.8	5.21	90	1.9	26.2	7.26	46	0°, 4¼ min.	Arfonad	29	Sluggish
						30.8	6.16	49	—15°, 1 min.		16	Unconscious
						35.9	5.29	55	—20°, 2 min.		24	Lethargic
						32.6	5.82	61	0°, 1 min.		13	Lethargic
7	75	29.8	4.32	92	1.3	16.3	7.98	42	0°, 5 min.	Arfonad	45	Unresponsive
						18.1	7.20	56	—15°, 1 min.		39	Lethargic
						16.7	7.79	46	0°, 2 min.		44	Normal
8	82	21.9	4.95	106	1.1	8.4	13.11	39	0°, 2 min.	Arfonad	62	Yawning, but responsive
						10.0	10.94	49	—25°, 1½ min.		54	"
						10.3	10.72	47	—25°, 3½ min.		53	"
						11.2	9.79	54	—30°, 5½ min.		49	Unresponsive
						12.3	8.97	81	0°, 15 min.		48	Responsive
9	75	25.7	5.32	110	1.4	12.5	5.05	60	+10°, 60 min.	Arfonad	51	Responsive
10	85	31.3	5.44	94	1.7	26.4	7.99	54	+20°, 10 min.	Hexameth.	16	Good contact
11	53	39.3	7.71	85	3.0	34.8	8.39	50	+10°, 3 min.	Hexameth.	11	Normal
						26.3	11.40	30	+10°, 6 min.		33	Nauseated
						35.8	8.15	48	—10°, 25 min.		9	Normal
12	46	36.6	8.03	183	2.9	27.6	10.49	98	0°, 3 min.	Arfonad	25	Angina, nausea
13	46	36.8	6.72	100	2.5	23.9	11.46	46	+10°, 24 min.	Hexameth.	35	Perspiring, Cheyne-Stokes resp., rational
14	32	38.3	7.17	100	2.7	29.1	8.83	40	+10°, 10 min.	Hexameth.	24	Normal

CBF, cerebral blood flow in cc./100 gm. of brain/min.; AVO_2, arteriovenous oxygen difference in vol. %; MAP, mean arterial blood pressure in mm. of Hg; $CMRO_2$, cerebral oxygen consumption in cc./100 gm. of brain/min.

in other studies, makes the conclusion inescapable that a critical point had been passed in these cases, although such was not always apparent from the data. This discrepancy suggests that the critical level may pertain to the circulation of specific brain areas concerned with alertness, consciousness, and some subjective reactions, rather than to the total cerebral circulation, the average of which is measured by currently available technics. The specific brain areas referred to have been shown to be subcortical in location and are probably identified with the reticular formation. Changes in blood flow of such relatively small brain areas may well be masked by the quantitatively more impressive demands of cerebral structures which are larger, but perhaps functionally of less immediate importance. Conversely, it is possible that changes in the blood supply of brain areas having little overt functional importance may, under certain circumstances, alter profoundly the average value of cerebral blood flow for the brain as a whole without producing obvious alterations in cerebral functions.

On the basis of the above consideration, one may postulate in elderly subjects a series of four cerebral circulatory types. In one group, the subcortical areas may share proportionately in a chronic general reduction of cerebral blood supply due to widespread cerebral atherosclerosis and associated with markedly reduced cerebral blood flow and with such symptoms as decreased alertness, tendency to excessive sleep, or even the agitation so commonly seen in senile individuals. In a second group, chronic cerebral ischemia due to atherosclerosis may locally affect subcortical areas more than other parts of the brain so that such symptoms are present in spite of an apparently adequate total cerebral circulation. In a third group, the vasculature of subcortical areas, although atherosclerotic and not able to respond enough to compensate for even mild hypotensive episodes, may nevertheless maintain adequate function under normal circumstances. These three groups cannot be expected to tolerate acute blood pressure reduction. In a fourth group, the variable distribution of the lesions of cerebral atherosclerosis may have essentially spared the blood supply to subcortical areas so that local compensation may occur in the presence of relatively severe acute hypotension, and reduction of total cerebral blood flow to remarkably low levels may have little apparent clinical effect.

It remains probable that, in individuals without cerebral atherosclerosis, anatomic and physiologic factors dictate the distribution of a rather fixed proportion of the total cerebral blood flow to subcortical areas; in such subjects, evidence of acute cerebral ischemia can be expected to appear at generally predictable levels of total cerebral blood flow, that is, "critical levels." It may be worthwhile in this connection to note that the symptomatology of early "acute cerebral ischemia" (yawning, sighing, anxiety, sphincter relaxation, possibly even convulsions, lethargy, and stupor) may well be ascribable specifically to subcortical structures.

SUMMARY AND CONCLUSIONS

Data were collected in 34 atherosclerotic individuals having unusually low rates of cerebral blood flow but clinically satisfactory cerebral function. In 14 of these cases the low cerebral blood flow was further reduced acutely by means of ganglionic blocking agents, combined with tilting. The existence of these subjects indicates that poor correlation between total cerebral blood flow and cerebral function is not rare. In the experimental group there was demonstrated a marked disparity between the degree of further reduction of cerebral blood flow and the appearance and/or severity of signs and symptoms of acute cerebral ischemia. It is postulated that this disagreement may be due to individual variation in distribution of cerebral blood flow, with symptomatology depending on critical circulatory levels in subcortical areas rather than upon quantitative changes in circulation of the brain as a whole.

The technical assistance of William K. Young, Marie D. Negron, and Julia V. V. Johnson is gratefully acknowledged.

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Electroencephalographic Effects of Intraventricular 5-HT and LSD in the Cat

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FIVE-HYDROXYTRYPTAMINE (serotonin, 5-HT) is a natural constituent of the brain with high concentrations in the hypothalamus, midbrain, caudate nucleus, and area postrema.[1,2] Extrinsic 5-HT injected into the lateral ventricle of the brain of the conscious cat causes profound behavioral changes, including lethargy, somnolence, and muscular weakness.[3,4] These observations assume importance in the light of suggestions that the tranquillizing drug, reserpine, exerts its central effects by releasing bound 5-HT in the brain.[2,5]

D-lysergic acid diethylamide (LSD 25, LSD) has received considerable attention as a psychosomimetic drug since its unusual actions were described ten years ago by Stoll.[6] The suggestion that it might exert its effects on the brain by antagonizing intrinsic 5-HT[7,8] followed the discovery that LSD blocked the action of 5-HT on rat uterine muscle.[9,10] Experiments to test the hypothesis have revealed that LSD will interrupt the behavioral effects of 5-HT or reserpine,[4] but in the dosages used extrinsic 5-HT did not appear to affect the action of LSD. Furthermore, substances other than LSD, including drugs which do not antagonize the effect of 5-hydroxytryptamine on peripheral tissues, were shown to have the same antagonistic effect on behavior. Conversely, several substances exhibiting 5-HT blocking actions in the periphery (Brom-LSD, methylmedmain, and 5-benzyloxygramine) did not antagonize the central effects of 5-hydroxytryptamine.[4,11] In human psychiatric patients low doses of LSD have been antagonized by very high dosages of 5-HT.[12]

Attempts to analyze the mode of action of 5-HT and LSD on the brain by electroencephalographic technics have generally depended on cortical records only and have led to conflicting reports. With cortical electroencephalographic records, LSD has caused flattening in all leads in the rabbit,[13,14] caused the disappearance of barbiturate spindles[15] or induced low-amplitude fast activity with occasional slow waves in the cat,[16] and has speeded the alpha rhythm or converted it into a beta rhythm[17] or has led to variable results in man.[18] LSD and 5-HT given together act synergistically in the cat.[19] According to recent work by Purpura,[20] desynchrony of the cortical electroencephalogram by LSD is attributable to inhibition of axodendritic synapses. This author has further shown in the cat that reserpine blocks the facilitatory or inhibitory effects of LSD upon some central neurophysiologic mechanisms. LSD also evokes "spontaneous" action potentials in the electroretinogram of the cat.[21] The injection of 5-HT intraventricularly in man caused an increase in alpha amplitude but not frequency[22] in the cortical electroencephalogram. Reserpine induces changes in cortical and subcortical electroencephalograms which have been regarded as an alerting type of response in the rabbit[23,24] and in the cat[25] while the animal is lethargic.

The present experiments were undertaken to study differential effects of LSD and 5-HT upon the spontaneous electrical activity of various cortical and subcortical regions of the brain which might be correlated with known behavioral changes induced by large doses of these compounds in the cat.[4] The effects of 5-HT on thresholds of arousal on stimulating the midbrain and bulbar reticular formations have also been tested. The results reveal that intraventricular injections of LSD or 5-HT, or both, induce certain characteristic reproducible effects at particular sites, some of which effects are antagonistic, while others are parallel and additive. It would appear that the electroencephalographic correlates of drug antagonism at the behavioral level depend on selective sensitization or inhibition of certain centers by each drug rather than on genuine pharmacologic antagonism at the same receptors within the brain.

MATERIALS AND METHODS

Twenty-six cats were employed in this study. After surgery under ether and local pro-

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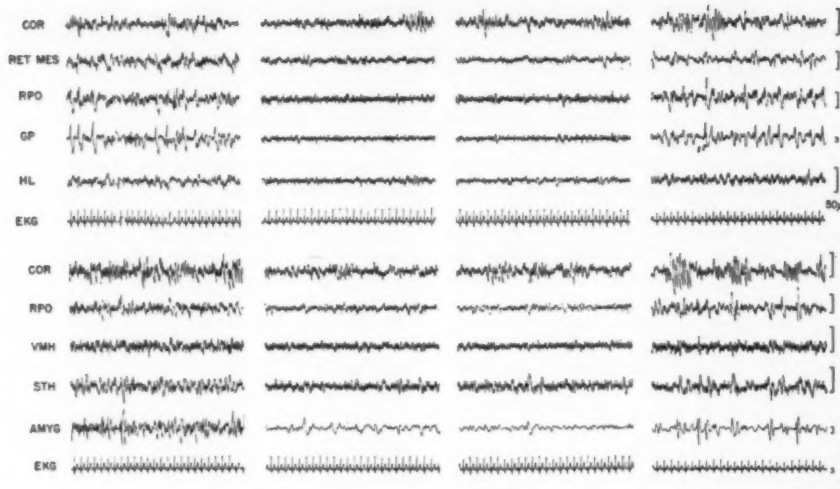

FIG. 1. *A.* Control record. *B.* One-half hour after 0.75 mg. 5-HT. *C.* Two hours after 5-HT. *D.* Six hours after 5-HT. Abbreviations employed in this and subsequent figures: AMYG, amygdala; CI, internal capsule; COR, cerebral cortex; DHA, dorsal hypothalamic area; EKG, electrocardiogram; EN, entopeduncular nucleus; GM, medial geniculate body; GP, globus pallidus; HL, lateral hypothalamic area; PED, cerebral peduncle; RE, nucleus reuniens thalami; RET MED, bulbar reticular formation; RET MES, mesencephalic reticular formation; RET TH, nucleus reticularis thalami; RPO, preoptic region; STH, subthalamic nucleus; VMH, ventromedial hypothalamic nucleus; VPL, ventroposterolateral thalamic nucleus; VPM, ventroposteromedial thalamic nucleus.

caine, the animals were immobilized with intravenous Flaxedil (gallamine triethiodide) and maintained under artificial respiration. Following a two-hour period of recovery from ether, racks of multiple concentric bipolar electrodes were positioned stereotaxically in various subcortical regions of the brain and a needle cannula was similarly inserted into the lateral ventricle. Phonograph-needle electrodes were fixed in tiny burrholes over the sigmoid gyrus of the cortex for bipolar cortical recording. Electroencephalogram and electrocardiogram (lead I) records were taken continuously for several hours with a Grass 6-channel inkwriting apparatus and the blood pressure was usually monitored continuously from the femoral artery. To determine the threshold of cortical arousal on direct stimulation of the mesencephalic and bulbar reticular formations, a biphasic wave form[26] with 50 μsec. between paired pulses was delivered. Voltage and milliamperage were monitored at each stimulation.

Five-hydroxytryptamine was employed as the creatinine sulfate salt at a dosage usually of 0.75 mg. (base) in 0.1 ml. unbuffered Ringer solution. This was washed into the lateral ventricle with 0.1 ml. Ringer. D-lysergic acid diethylamide tartrate was similarly employed at a dosage of 0.8-1.0 mg. (salt). The exact position of the cannula tip, as well as the electrode sites, were ascertained histologically.

RESULTS

5-hydroxytryptamine alone. Representative effects of a single intraventricular injection of 5-HT on the spontaneous electrical activity of the cerebral cortex and seven different subcortical areas are shown in figure 1. The vertically-spaced segments of the two horizontal groupings were recorded alternately, and they represent different regions of the same brain at approximately the same time. At one-half hour *(B)* and two hours *(C)* after injection there is seen a generalized reduction in amplitude, whereas the initial pattern and amplitude are largely recovered at six hours *(D)*. The most dramatic changes are seen in the amygdala, globus pallidus, and subthalamic and preoptic areas in which high-amplitude activity and spikes observed before treatment were completely absent at one-half hour and two hours and were replaced by a low-amplitude regular 10-12/sec. (alpha) frequency rhythm.

Characteristically, 5-HT reduced the amplitude of the activity in almost every region of the brain so far studied. An exception was

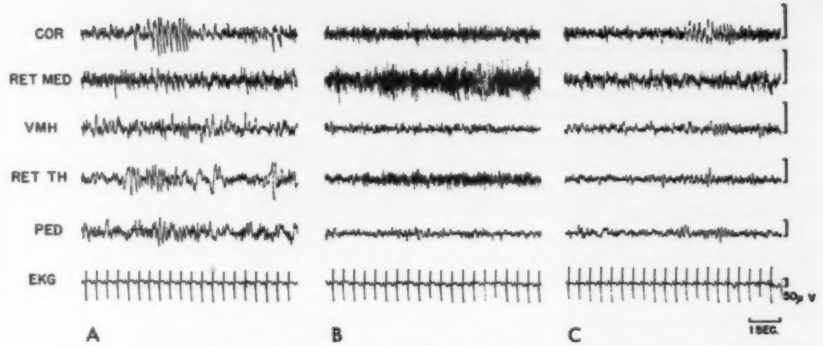

FIG. 2. *A.* Control record. *B.* One-half hour after 0.75 mg. 5-HT. *C.* Two and one-half hours after 5-HT.

the medullary (bulbar) reticular formation in which long spindle-like bursts of up to 45 per second high-amplitude activity were encountered in about 50 per cent of the cats. This is illustrated in figure 2, in which the frequency seen in the bulbar reticular formation was also observed in the reticular nucleus of the thalamus. These bursts of increased amplitude fast activity were not seen in the mesencephalic reticular formation. As mentioned later, they were also encountered in the bulb with LSD and were observed to augur an immediate sharp rise in blood pressure.

Typically, the depressed activity in midline diencephalic areas, such as ventromedial, posterior, and dorsal hypothalamic nuclei, was maintained in a fast state and did not show the slower 8 to 12 per second frequencies which were seen in the more lateral regions, including putamen, pallidum, and subcortical rhinencephalic areas. Other areas in which an alpha rhythm was observed after 5-HT included the internal capsule, entopeduncular nucleus, cerebral peduncle septum, subthalamus, and the thalamic relay nuclei, ventroposteromedial (VPM), ventroposterolateral (VPL), and medial geniculate body.

In seven experiments the thresholds of arousal on stimulating sites in the mesencephalic and bulbar reticular formation were obtained before and at various intervals after injecting 5-HT. In a limited number of cases the pressor threshold was also determined on stimulating the same sites. The arousal threshold on mesencephalic stimulation varied from 2.0 to 4.5 volts, while in the bulb it varied from 2.7 to 4.2 volts in different animals. There was no change in either bulbar or mesencephalic thresholds of arousal after 5-HT.

LSD alone or followed by 5-HT. Figure 3 reveals the dramatic effects of intraventricular LSD on electroencephalographic activity in the preoptic area and especially the globus pallidus. Two paper speeds are shown, with each horizontal tracing respresenting a continuous record. It is apparent that a high-amplitude 50 per second activity developed or was accentuated in preoptic and pallidal channels after LSD, and that the activity was further augmented following a second dose of LSD. (This fast synchronized discharge was invariably seen in pallidum and/or putamen after LSD.) Meanwhile the cortical electroencephalogram was slowed and frequent spindles appeared, as was nearly always our experience with LSD. The activity in the mesencephalic reticular formation and the dorsal hypothalamic area was reduced considerably in amplitude. The heart was markedly slowed and the electroencephalogram showed a rotation of the QRS axis with T-wave inversion. The enhanced 50 per second activity in the pallidum and preoptic region had largely disappeared before the second LSD which was injected two hours after the first. At 30 minutes after the second LSD a 5 mg. intravenous dose of pentobarbital completely obliterated the 50 per second activity and replaced it with a slow four per second rhythm.

Figure 4 shows the effects of LSD on a different array of subcortical centers in another cat. The changes were relatively minor, except in the medial geniculate body in which, at one hour after LSD, a brief localized seizure was observed followed almost at once by a depression in blood pressure. The electroencephalographic activity in this channel remained rapid (50 per second) thereafter, but the seizure was not repeated even after a second injection of LSD.

Although it is not apparent in channel 2 of figure 4 after LSD, the medullary reticular

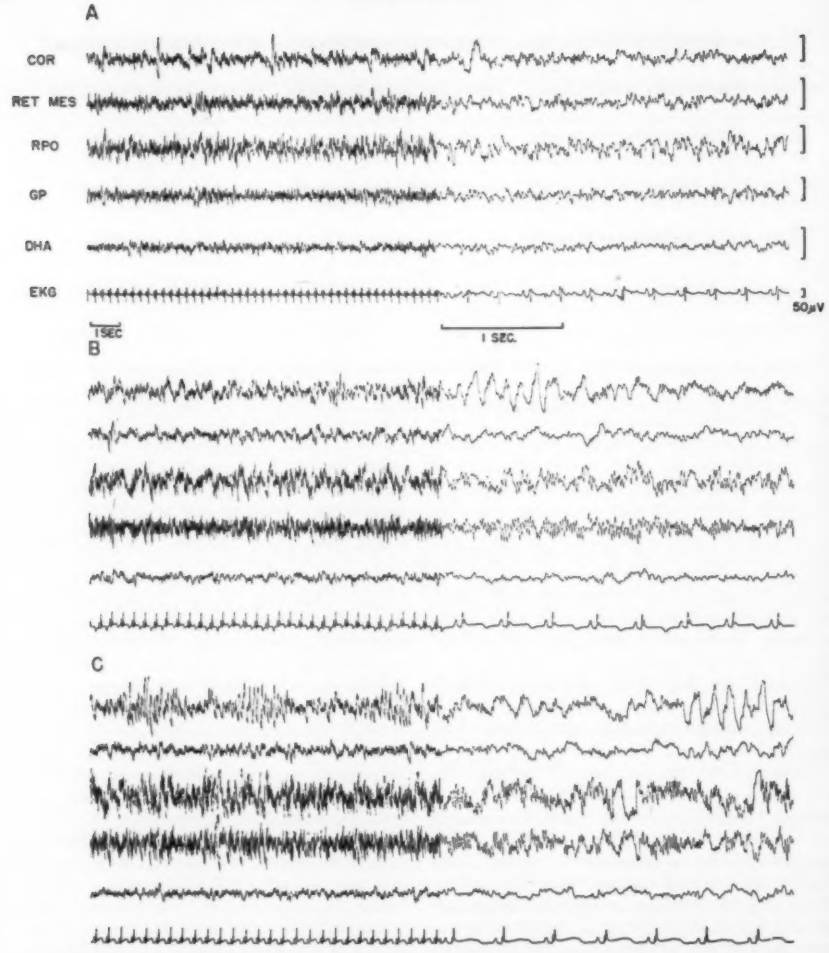

FIG. 3. A. Control record. B. Ten minutes after 1 mg. LSD. C. Six minutes after second LSD (0.75 mg., two hours after first LSD).

formation often revealed prolonged spindle-like bursts of 15 to 45 per second activity similar to that following 5-HT in figure 2B. These were correlated with rises in blood pressure and will be reported later.

The general blood pressure response to intraventricular LSD was a rapid drop of 15 to 20 mm. (One to five minutes), rising slowly to pre-injection levels in 10 minutes. Approximately 15 to 18 minutes after injections, frequent periodic pressor fluctuations (0 to 80 mm.) would occur for approximately 15 to 20 minutes. The bradycardia began simultaneously with the depressor effect and lasted more than one-half hour, well into the pressor phase.

Besides the pallidum-preoptic effect, LSD almost invariably enhanced amygdaloid electroencephalographic activity by increasing the amplitude and regularity of a 50 per second rhythm (figure 5). Subsequently, 5-HT evoked a slow rhythm of 8 to 10 per second. Other regions which occasionally showed the 50 per second frequency following LSD treatment were the subthalamus, the internal capsule (fasciculus lenticularis-?), and lateral hypothalamic area.

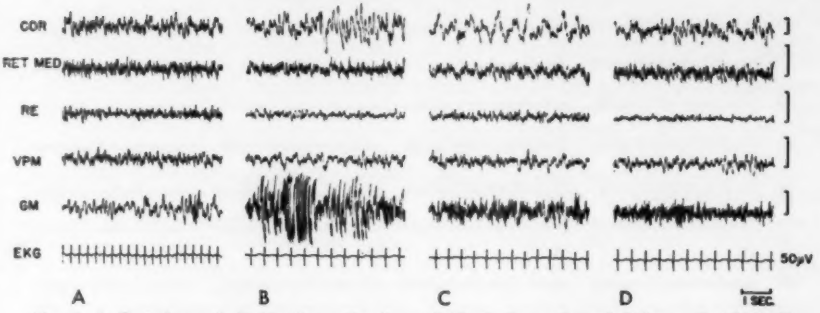

FIG. 4. *A.* Control record. *B.* One hour after 1 mg. LSD. *C.* One and one-half hours after LSD. *D.* Fifteen minutes after second LSD (1 mg., two hours after first LSD).

Since the effects of LSD were of short duration and the effects of 5-HT were slow in developing, electroencephalographic changes following this sequence were difficult to interpret and few such experiments were conducted.

5-HT followed by LSD. In a great majority of the regions studied, LSD depressed the amplitude of the spontaneous electroencephalographic activity and, if given after 5-HT, it further reduced the already depressed activity. This is illustrated in figures 6 and 7.

The two horizontal sequences in figure 6 are from two different cats under similar timing conditions. B and B' show the changes achieved 35 minutes after intraventricular 5-HT; C and C' show the probable maximal influence of effective dosages of 5-HT, while D and D' reveal the additive or opposing effects of LSD. With 5-HT the cortex was either reduced in amplitude, or it developed a 10 per second alpha rhythm without spindles, while LSD evoked slowed activity or spindles. The activity of the bulbar reticular formation (RET MED) was not altered appreciably by either agent in these animals. The activity in ventromedial and dorsal hypothalamic regions and the cerebral peduncle was diminished in amplitude and/or frequency by 5-HT and further reduced by LSD, quite dramatically in the last two regions. In the internal capsule and entopeduncular nucleus, 5-HT induced a regular 10 to 12 per second alpha rhythm which was lost in favor of a lower amplitude faster activity after treatment with LSD. In this series neither agent drastically altered the record of the VPL thalamic nucleus.

A very different effect in this regard is observed in figure 7. In 7B insufficient time had elapsed for a maximal effect of 5-HT, as evidenced by the slow waves in the cortex, though reduced activity in the ventromedial hypothalamic nucleus and enhanced activity in the medullary reticular formation are already discernible. LSD was given before 5-HT had time to reach maximal effectiveness, and 12 minutes later a dramatic long-lasting high-amplitude activity is observed in the VPL thalamic nucleus.

The regions in which 5-HT and LSD exerted parallel and additive influences include the ventromedial, dorsal, lateral, and posterior hypothalamic areas, such thalamic nuclei as reuniens, reticular, ventromedial, and occasionally the ventroposteromedial, the cerebral peduncles, subthalamus, and mesencephalic re-

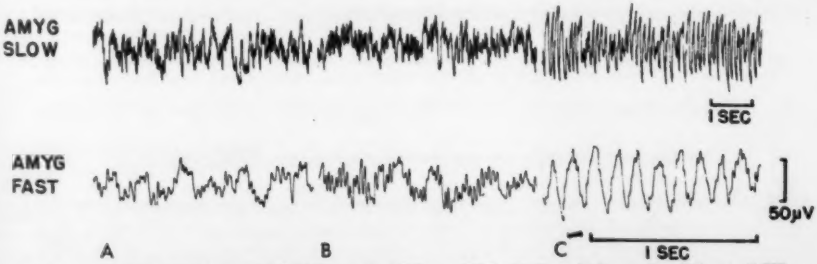

FIG. 5. *A.* Control record. *B.* One-half hour after 0.8 mg. LSD. *C.* On-half hour after 0.7 mg. 5-HT (two and one-half hours after LSD).

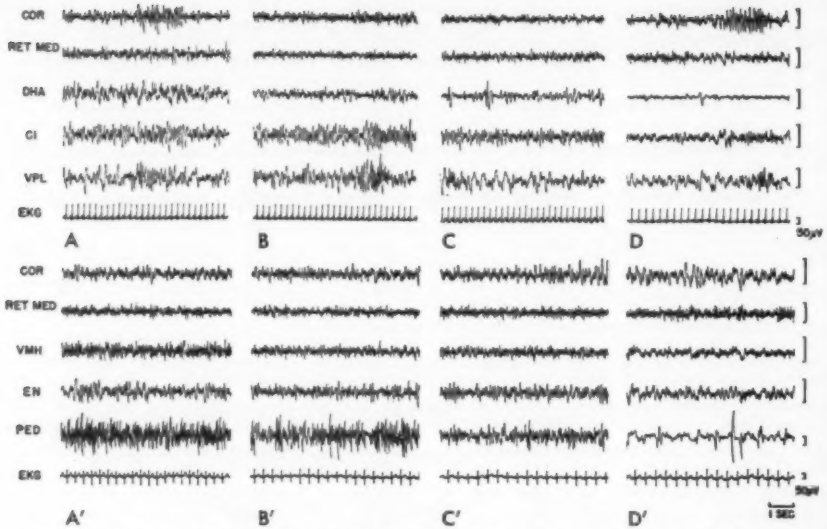

FIG. 6. *A, A'*. Control records. *B, B'*. One-half hour after 0.75 mg. 5-HT. *C, C'*. One and one-half hours after 5-HT. *D, D'*. One-half hour after 1.0 mg. LSD.

ticular formation. Antagonistic or opposite effects of the two drugs were observed in the putamen and pallidum, the subthalamus, the amygdala, and preoptic region. Localized high amplitude, almost seizure-like activity following LSD was observed occasionally in the thalamic relay nuclei VPL and the medial geniculate body.

DISCUSSION

Intraventricular 5-HT in the cat caused temporary electroencephalographic changes that resembled those induced by reserpine in the rabbit.[23,24] Neither agent produced a "sleepy" pattern, but both evoked in certain subcortical regions a prolonged alpha rhythm which is characterized by a frequency of eight to 12 per second in the cat and three to seven per second in the rabbit.[27] Similarly in man, Sherwood[22] has shown that 5-HT enhances the amplitude of the cortical alpha rhythm. The doses of 5-HT used were very high, and it should be remembered that some of the actions observed may not base their effect primarily on the neurons but may be mediated through local constriction of cerebral blood vessels.

The alpha rhythm in the cat and man is characteristic of the relaxed but not sleeping state, and probably it involves essentially the

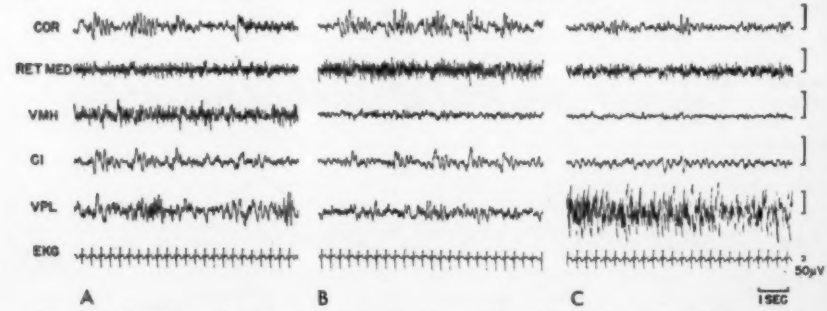

FIG. 7. *A*. Control record. *B*. Twenty minutes after 0.7 mg. 5-HT. *C*. Twelve minutes after 0.8 mg. LSD (one hour after 5-HT).

thalamus[28,29] and recruitment along the diffuse projection system of Dempsey and Morison.[30] The enhancement of the alpha rhythm by 5-HT may have been effected by inhibition at synapses of impulses that would interrupt the rhythm. 5-HT did not raise the threshold of cortical arousal on stimulation of the reticular formation itself, but it did markedly lower the amplitude of activity in the midbrain reticular formation, suggesting some inhibitory influences further peripherally along afferent pathways. It has been suggested that reserpine acts at least partially in such a manner,[31] and this parallelism is consistent with the hypothesis that reserpine functions by releasing 5-HT from binding sites.[2,5]

The present observation that the onset and duration of depression by 5-HT of amplitude of electroencephalographic activity in amygdala and pallidum and their projection pathways parallels stages of behavioral lethargy may be related to observations with other drugs at the same sites. Reserpine exerted marked stimulating effects on rhinencephalic electrical ground activity,[23] and inhibited hippocampal protein metabolism,[25] hippocampal seizures,[32] and electrical self-stimulation when the electrode was in the amygdala.[33] Certain effects of chlorpromazine[34] and insulin coma[35] have been related to seizure activity in the amygdala and/or hippocampus. In the human basal ganglia reserpine has converted a fast frequency wave sequence to a much slower rhythm.[36] Symptoms of basal ganglia involvement (parkinsonism) have been observed in man following either reserpine or chlorpromazine treatment.[37]

In contrast to some observations reported here, Schwartz and co-workers[16] did not find any antagonism between 5-HT and LSD relating either to behavior or the electroencephalogram. This is undoubtedly due to their use of a small fraction of the amount of LSD employed by us, while the doses of 5-HT were of the same order of magnitude. The high dosage of LSD was necessary to produce the behavioral changes,[4] and the duration of electroencephalographic changes induced by LSD correlates well with the known duration of sham rage. Although the depression in amplitude of electroencephalographic activity in thalamic, hypothalamic, and mesencephalic nuclei near the midline may in some way condition the behavior, parallel effects on these centers are seen with 5-HT. The rage phenomenon seems more likely to be a correlate of the hyperactivity in the amygdala and basal ganglia. Localization of sham rage mechanisms in the temporal lobe is not without precedent. Several investigators[38–40] have induced or prevented sham rage by the appropriate manipulation of this region in monkeys and cats. The opposite electroencephalographic effects of 5-HT, temporally related to sedation, add weight to the behavioral importance of these regions. The theory that LSD exerts its effect on behavior by antagonizing intrinsic 5-HT is weakened by the observation that at many sites they have the same effect on electroencephalographic activity.

The question of whether the cat suffers LSD hallucinations is impossible to answer at the present time. If such should be the case, a possible physiologic explanation is Purpura's proposal[20] that LSD facilitates axosomatic synapses while depressing axodendritic ones. The thalamic relay nuclei are of the former type, and the high amplitude activity occasionally encountered in VPL and the medial geniculate nucleus might be a result of axosomatic enhancement. Others have pointed to LSD facilitation in the optic system[21,17] as a suggested mechanism for hallucinations. Since hallucinations are subjective phenomena, their neurophysiologic correlates must be evaluated in clinical studies.

SUMMARY

An electroencephalographic study of the effects, in the brain of the immobilized conscious cat, of intraventricular injections of 5-HT and lysergic acid (LSD) reveals the following:

The cortical electroencephalographic effects, desynchrony with 5-HT and spindles with LSD, give little indication of more profound changes occurring in subcortical regions.

Both 5-HT and LSD characteristically depress the amplitude of activity in medial hypothalamic and thalamic nuclei and stimulate the bulbar reticular formation.

LSD evokes a high amplitude 50 per second rhythm in the pallidum, putamen, amygdala, and their propection systems, a change which roughly parallels in time the known duration of sham rage behavior from a similar dosage of the drug.

5-HT retards the electroencephalographic activity of the same regions generally to an eight to 12 per second alpha rhythm, and again the temporal aspect of the changes correlates well with the known duration of lethargic behavior evoked by the drug.

Doses of LSD which temporarily reverse the longer lasting behavioral lethargic effects of

5-HT similarly antagonize briefly the 5-HT effects on the electroencephalographic activity of pallidum, putamen, and amygdala.

It is suggested that "LSD-induced" high-amplitude bursts of electroencephalographic activity in certain relay nuclei of the thalamus may contribute to aberrancies of sensation.

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The Cerebral Collateral Circulation

2. Production of Cerebral Infarction by Ischemic Anoxia and its Reversibility in Early Stages

D. Denny-Brown, M.D. and John S. Meyer, M.D.

IT IS COMMON clinical experience that a remarkable degree of functional recovery may occur in a neurologic disorder resulting from thrombosis and insufficiency[1] of the major cerebral vessels. Indeed, in syndromes due to insufficiency of the basilar and carotid arteries the intermittent nature of the symptoms characterizes the disorder.[1–4] For example, we have recently treated an elderly woman suffering from occlusion of the internal carotid artery who has had nine transient episodes of complete hemiplegia and hemianopia of one to one and a half hours duration, with complete recovery on each occasion. The tenth attack lasted for 48 hours and some spastic weakness of the arm has persisted.

Both clinical and experimental evidence indicate that, in most types of such transient paralysis, the onset of symptoms is due to a fall in systolic blood pressure reflected in the supply to an area that is already compromised by stenosis or occlusion of its major tributory.[2] Under these circumstances recovery from the resulting hemodynamic crisis may reflect only the rapid recovery of adequate systolic blood pressure. In other circumstances recovery of function occurs in spite of continuation of diminished cardiac output for many hours or days. In this case, the collateral circulation may itself have adjusted to the state of insufficiency. A fall of systolic pressure of sufficient duration, for example, that is related to gastrointestinal hemorrhage[2] can certainly lead to catastrophic infarction. In embolism the area of infarction is also greatly variable, manifestly due to variations in collateral supply.

It is, therefore, desirable to learn more of the dynamic adjustments of collateral vessels in the brain, with a view to better definition of the factors that increase collateral blood flow when a main vessel is occluded. In previous communications[5,6] we have reported an experimental analysis of collateral circulation in terms of the fall and recovery of oxygen tension in the relatively ischemic area and in terms of the reactive vasodilation of collateral vessels. The level of systolic pressure, the level of intraluminal pressure, the oxygenation of arterial blood, the vascular resistance of the ischemic area, and, to a less extent, metabolic by-products of anoxia in the ischemic area emerged as important factors. The present study is devoted to a close examination of events in the vessels of the ischemic area, seeking to define the local factors underlying ischemic response, increased vascular resistance, and infarction.

An attempt has been made to produce varying degrees of failure of the collateral circulation and to examine the resulting functional impairment in terms of neuronal injury as indicated by the electrocorticogram and steady potential (S.P.). The validity of these technics has been critically reviewed previously.[7] Vascular damage was judged by observations of blood flow in the cortical vessels with a microscope and by photomicrography. In many experiments changes in vascular permeability were studied after the intravenous injection of trypan blue, as used by Broman and others.[8–10] Attempts were made in most experiments to improve any functional damage to the cortex or its blood flow by restoration of the blood pressure and by the administration of oxygen or of heparin solution intravenously.

Neuronal and vascular damage were also analyzed in terms of any change in local oxygen tension, as determined by the polarographic method,[5–7] and compared to that produced by prolonged nitrogen breathing for purposes of comparison. In three experiments histologic studies of the brain after removal, fixation, and staining were correlated with the microscopic and polarographic observations made in vivo.

MATERIAL AND METHODS

The investigation was carried out on 33 monkeys (Macacus mulatta). Observations on

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Opinions expressed are those of the authors and do not necessarily represent those of the Department of the Navy.

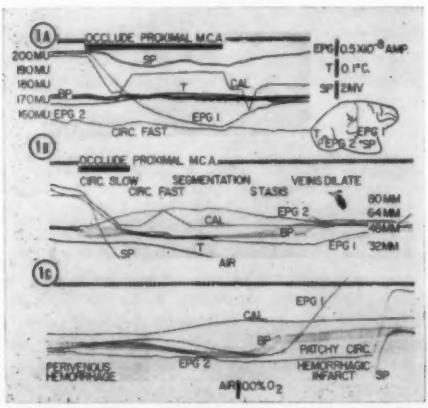
the factors influencing adjustments in the collateral circulation prior to its failure have been reported in a previous communication, together with a detailed account of the technics used in this study.[6] Continuous records of the oxygen tension of several small areas of cortex were made by a modification of the polarographic method (EPG). The electrocorticograph and steady potential (S.P.) were recorded with chlorided silver electrodes. The electrocorticogram was recorded with a Grass III D electroencephalograph and in some experiments with an Offner Type D eight channel polygraph in which four channels were used for D.C. recording. In later experiments the Offner polygraph was substituted for the galvanometer and kymograph camera, permitting concurrent recording of electrocorticogram, S.P., EPG, blood pressure, and electrocardiogram with the inkwriter on paper. A dissecting microscope was used for observations of the pial vessels, the exposed cortex being covered with a thin layer of mineral oil warmed to body temperature. Photomicrographs were made in color with a Leica camera and a 20 or 48 mm. microtessar lens fitted to a focusing tube of approximately 30 cm. in length. The resulting magnification was 25 to 75 times. For illumination a 108-watt ribbon filament Mazda lamp supplied by Bausch and Lomb was used, the light being filtered through alum solution. The beam did not give any appreciable warmth that could be felt with the bare hand.

The blood pressure was altered by raising and lowering the feet on a small tilt-table, by removal and reinjection of venous blood, and by the use of adrenalin. Heparin was injected intravenously in doses of 1,000 units (10 mg.). A saturated solution of trypan blue was injected in divided doses depending on the weight of the animal and the duration of the experiment. The usual dose was 6 to 10 ml. In three experiments blocks of formalin-fixed brain were embedded in celloidin and paraffin, sectioned, and stained with hematoxylin and eosin, luxol fast blue, cresyl violet, and by the Heidenhein and Loyez methods for myelin.

RESULTS

Catastrophic Failure of the Cerebral Circulation

As others[11] have also found, occlusion of the



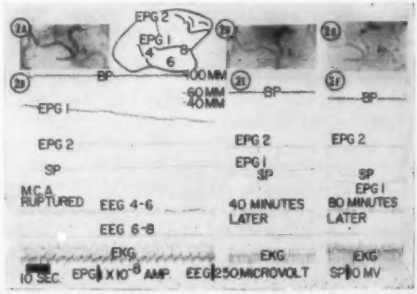


FIG. 1. Three records from same experiment; *A*, *B*, and *C* are continuous. In *A* occlusion of the middle cerebral artery for 3½ minutes with a low blood pressure resulted in a reversible injury potential (S.P.) associated with severe hypoxia (EPG 1) but without vascular damage. In *B* repeat occlusion for 1½ minutes resulted in a rapidly developing injury potential, segmentation, and stasis in isolated small venules emerging from cortex. In *C* perivenous hemorrhages and hemorrhagic infarction appeared. Breathing 100 per cent oxygen restored B.P. and a patchy cortical circulation with a rise in both EPG 1, EPG 2, and of S.P. Electrode positions are shown on brain diagram and arrow indicates vessel measured. Calibration of EPG, T, and SP electrodes to the right of *A*. Vessel diameter (CAL) in micra is noted to the left of *A*. Femoral blood pressure (BP) is calibrated on record *B*. Initial reading of EPG 1 = 3×10^{-6} amps. T = Microthermistor. Changes in circulation are noted on the record and a diagramatic representation of a dilated venule with stasis is drawn on record *B*. Time marker at top of record indicates 6 second intervals.

FIG. 2. *A*, *B*, and *C* are photomicrographs of the postcentral gyrus (near EPG 1 electrode in brain diagram) taken at intervals corresponding to the three strips of record marked *D*, *E*, and *F*. *A* shows cortical vessels prior to rupture of the middle cerebral artery, and *B* 40 minutes after rupture to show segmentation and stasis. Record *D* shows reduction in EPG 1 oxygen availability and *E* shows further reduction with isoelectric electrocorticogram and an injury potential (SP). EPG 2 in bordering area shows little change. Photo *C* was taken 80 minutes later to show increased stasis and hypoxia in the Sylvian area.

Brain diagram shows electrode positions. Calibration of time, EPG, electrocorticogram and SP at base of record and of blood pressure on record *D*. Diameter of vein shown by upper arrow is 65 micra. Initial reading of EPG 1 = 8×10^{-6} amps.

middle cerebral artery in the healthy monkey with normal blood pressure has surprisingly little effect on the area of brain supplied by this vessel. Large anastomoses with the anterior and posterior cerebral arteries provide a collateral circulation for the reduced needs of the cortex of the anesthetized animal. Nevertheless, a fall in tissue oxygen potential occurs in the central part of the affected area, reversed in the next minutes by increased flow in the anastomotic vessels, as described in earlier papers.[5,6] Reduction of systolic blood pressure abolished this delayed adjustment,[5] but nevertheless the occlusion has to be maintained for approximately one hour or longer in order to produce a subsequent infarct.[11] In order to induce evidence of tissue damage, within minutes a drastic reduction of blood pressure was found to be necessary. Prolonged or repeated occlusion of the proximal portion of the main trunk of the middle cerebral artery then regularly caused varying degrees of neuronal and vascular injury, including suppression of the electrocorticogram, an injury potential, and slowing, segmentation, and eventually stasis in the pial circulation. In the presence of a low blood pressure, as in figure 1, occlusion of the main trunk of the middle cerebral artery for three and a half minutes resulted in severe hypoxia in the temporal region (EPG 1) without a significant increase in blood flow from the posterior cerebral arteries (EPG 2 and T). An injury potential occurred (S.P.) without any sign of damage to the pial branches of the middle cerebral artery which showed only a reduction in caliber (CAL). When the vessel was released, the oxygen tension in the Sylvian region rose (EPG 1) and there was recovery of the injury potential (S.P.). The close relationship of injury potential to local anoxia following vascular occlusion in this and other experiments suggests that an injury potential is initiated by local anoxic damage to neurons. If the restoration of circulation is not delayed, the injury may be reversible.

After the initial ischemic neuronal injury, the threshold is lowered for each repeated occlusion. A similar lowering of the threshold for neuronal injury is also seen in anoxic anoxia.[12] For example, in figure 1B occlusion of the middle cerebral artery for the second time again produced severe tissue hypoxia in the Sylvian region (EPG 1), but the latency for the development of the injury potential (SP) was shortened. The collateral blood flow (CAL,T) failed to show any effective response except for a slightly increased flow in the small branches of the posterior cerebral artery as judged by EPG 2. The severe embarrassment of total cerebral blood flow was associated with hyperpnea reflected in the blood pressure record. In spite of release of the middle cerebral artery, the blood flow slowed and segmentation of the column of blood appeared in the terminal venules (15 to 60 micra in diameter). As the blood flow ceased, these vessels became grossly dilated to twice their normal diameter at points of emergence from cortex and were distended with packed red blood cells (see diagram on record B of figure 1), being collapsed in the remainder of their course. Concurrently, the smaller arteries became greatly narrowed or even collapsed completely. Segmentation of flow regularly preceded stasis and the sequence is shown in photomicrographs A, B, and C of figure 2, in D of figure 3, and C and D of figure 4. In figure 2 the arrows show the development of segmentation and stasis in a terminal pial venule and vein following rupture of the middle cerebral artery. In this type of experiment, terminal venous stasis was a constant component of infarction and tended to precede arterial segmentation and stasis. When arterial segmentation and stasis occur, they are seen first in the small arterio-arterial anastomoses, as shown in the series of photomicrographs shown in B, C, and D of figure 3. Occlusion or rupture of a main cerebral vessel with a critical reduction of blood pressure, as in figure 4D, results in segmentation and stasis in larger arterial trunks.

Continued occlusion of the middle cerebral artery, or its rupture, in the presence of a very low blood pressure results in progressive clumping of the column of blood and eventual blocking of arteries and veins of all sizes, with a well defined line of demarcation between infarcted and relatively anemic brain. In the infarcted zone all blood flow ceases except rarely a sluggish flow continues in a few arteries and veins. In areas of fresh arterial infarction and for six to eight hours thereafter, the oxygen readings are reduced to 5 to 20 per cent of the control readings prior to occlusion. In the bordering zone the oxygen readings fluctuate above and below the steady state, depending on anatomic variations in the collateral circulation and the level of the systolic blood pressure (figures 1, 2, 3, 4, 6, and 7). The line of demarcation between normal and infarcted brain is not a stable one. Lowering the blood pressure or nitrogen breathing causes

an increase in the area of infarction.

This series of events reflects a degree of vascular damage that is catastrophic both in terms of tissue damage and in terms of vascular recovery. Though arterial flow may be restored, widespread stasis and vascular occlusion are likely to result. It is cited here only as evidence of the series of events associated with circulatory collapse with complete failure of collateral supply, a circumstance that must be rare in the course of vascular disease.

NEURONAL DAMAGE

The first sequel of severe cortical ischemia is slowing of the electroencephalogram with reduced amplitude, but occasionally an increase in voltage, that appears within eight to 15 seconds and is localized to the area of cortex supplied by the occluded vessel (figures 2, 6, and 7). Continued occlusion results in focal suppression of the electroencephalogram and the development of an injury potential in the ischemic zone. The injury potential ap-

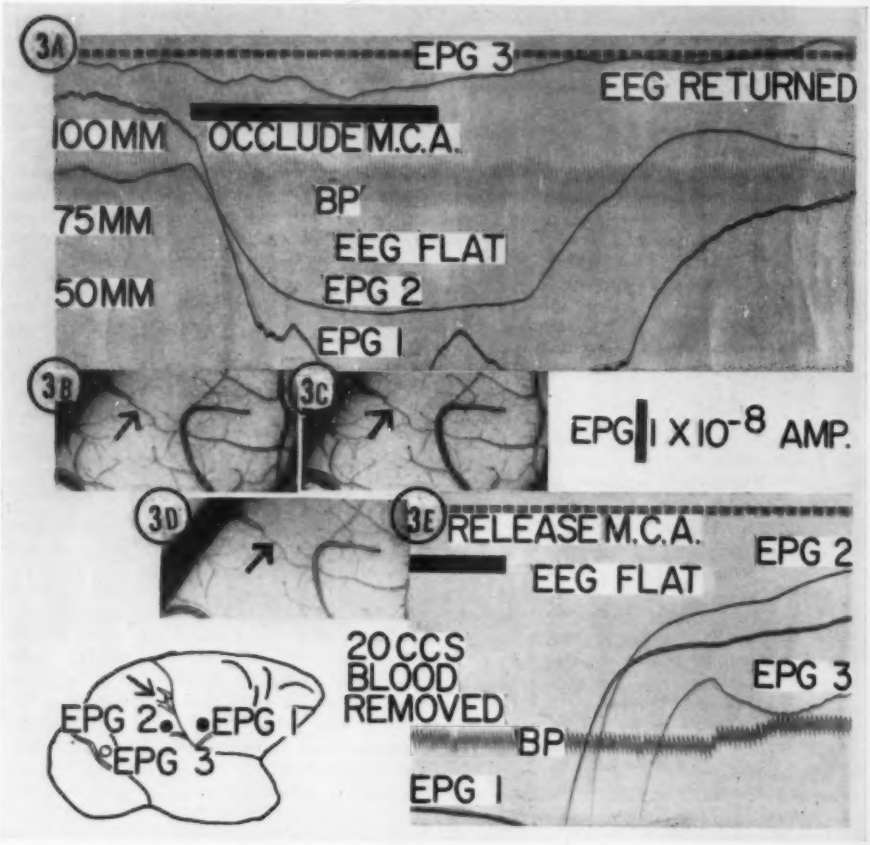


FIG. 3. *A* and *E* are two records from the same experiment to show reversibility of early neuronal and vascular damage; *B*, *C*, and *D* are photomicrographs of cortical vessels taken concurrently. *A*. Brief occlusion of middle cerebral artery produced severe hypoxia in the Sylvian region (EPG 1 and 2) without increase in occipital blood flow (EPG 3). The electrocorticogram became isoelectric but was restored after an increase in the cortical oxygen tension when the middle cerebral artery was released. *B* is a photomicrograph of an arterio-arterial anastomosis (measuring 50 micra) shown by arrow on brain diagram. *C* shows narrowing after occlusion of middle cerebral artery. *E* shows a diffuse, severe reduction of oxygen availability with reocclusion and a low blood pressure. *D* shows segmentation of flow in the arterio-arterial anastomosis.

pears two to five minutes after the first occlusion, depending on the effectiveness of the cerebral collateral circulation. The S.P. shift reflects a depolarization of neural tissue that may occur in the absence of stasis or thrombosis of vessels. Previous episodes of ischemia lower the threshold for neuronal injury and under such circumstances an SP shift may develop within 18 to 50 seconds after occlusion of the vessel (figure 1). Restoration of local circulation by release of the vessel or by raising the blood pressure results in a varying degree of reversal of the S.P. and electroencephalographic changes depending on the duration and severity of the localized hypoxia (figures 3A, 6, and 9). If severe infarction has occurred the electroencephalographic and S.P. changes are irreversible, but if infarction is less severe and some blood flow can be restored to the injured area, the rise in the local oxygen tension is associated with a return of the S.P. toward the steady state (figure 1B). The electroencephalogram may continue to show slow activity and diminished amplitude after recovery of the S.P.

VASCULAR DAMAGE RESULTING FROM INTERMEDIATE GRADES OF ISCHEMIA

In the presence of less drastic reduction of systolic blood pressure, occlusion of the middle cerebral artery produces a less severe fall in tissue oxygen tension in the area of supply. The collateral circulation may make poor response to the tissue demand, with corresponding loss of electroencephalographic potential and S.P. shift. If, under these circumstances, occlusion is prolonged for a period of over five minutes or is repeatedly applied for lesser intervals, a type of vascular change is induced that differs in many respects from that described above. During such occlusions there may be surprisingly little change in the cortical vessels in any part of the territory supplied by the artery, except the changes in caliber that we have described in a previous paper.[6] The cortex preserves its natural pinkness, and the rate of flow is still so rapid that the movement of red cells cannot be seen except in the few capillaries that are visible in the meninges. On release of the vessel there is also no change except in vascular diameter, but as this seldom exceeds one-tenth even in reactive hyperemia it is not obvious. When the oxygen potential remains very low with well marked S.P. shift, for more than five minutes an additional change is seen. This takes the form of a darkening and thickening of the column of blood in one of the smallest terminal branches of a vein where it emerges from the cortex and in its short segment of meningeal course before it is joined by another such venule. Within the next five minutes, this short column of blood gradually broadens and darkens until it is almost black. In this time it commonly breaks into segments, which can now be seen to be formed of static, tightly packed red cells, often in rouleaux formation. Clumping of this type is different from the segmentation seen with simple circulatory failure, in that the clumps of red cells are more dense and appear darker and flow continues in the remainder of the vein after it is joined by the next branch. The original small venule, originally 10 to 20 micra in diameter, is swollen to 40 or 50 micra (figures 5A, 7C and D, 9, and 10).

This phenomenon clearly represents the result of stasis in the part of the cortical capillary net underlying the small venule, with oozing of clumped red cells into its venous outlet. At first, such stasis is seen only in single venules at isolated points in the ischemic area, 1 to 10 mm. distant from one another, the intervening vessels being unaffected. If the circulation is now restored no further change occurs in periods of observation up to four hours, except that the area of cortex immediately surrounding the microstasis becomes relatively pale in the next 15 minutes following its appearance. If ischemia is continued or renewed at this same level these venules do not change, but more isolated venules of the same size are affected in the same manner in every part of the area. Sooner or later another contiguous venule draining the area is affected in the same manner. The stasis on the venous side of the capillary net, therefore, appears in punctate manner and is worsened by the appearance of more foci of stasis and by extension of those appearing first. When two confluent venules are affected, flow in their common trunk then also becomes static as far as the junction of the next tributory vein (figure 5A). With worsening of the condition as a result of further repetition of ischemia, larger veins draining a whole area become engorged with dark anoxic segmental masses of clumped cells (figure 5B). Only at this stage does stasis begin to appear in small arterioles entering the cortex, all the arterial net having been unaffected up to this point (figure 5B).

The tissue oxygen potential ultimately may recover to a remarkable degree during the early stages of such microstasis, if local blood flow improves, presumably because the affect-

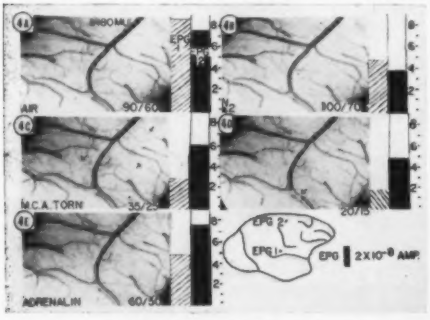
ed points are very small in relation to the size of the electrode. When many veins become affected, as in figure 5B, the EPG then fails to recover from zero level and infarction of the tissue is complete.

In this whole process white thrombi are not seen. The microstasis does not appear to be associated with thrombosis in any part of its formation stage. Capillaries are rare in the meninges, but where they were involved it was clearly evident that stasis began on the venous side of the capillary (figure 6I) and spread to its junction with a venule. In such capillaries, and occasionally in cortical venules, the stasis could be reversed by raising blood pressure by administering adrenalin (figure 6, III, IV) provided the stasis had not been present more than about 15 minutes. Occasionally oxygen breathing reversed some recent microstasis. The administration of heparin in some experiments appeared to make the production of further microstasis difficult in the following three to four hours of observation, but within the time limits of these experiments did not reverse microstasis already present unless there was also an associated rise of blood pressure.

Cortical Edema Associated with Stasis

Further information regarding the phenomenon of microstasis was obtained by saturating the circulating blood with trypan blue before ischemia. This procedure darkens the appearance of all the cortical vessels as seen with a binocular microscope. As a result the first stage of stasis, the change in color, is no longer apparent. Within five minutes of the estimated onset of microstasis in a venule, however, a blue haze begins to appear in and around each of the neighboring veins and venules within a radius of about 3 to 5 mm. from the affected vessel. Within another five minutes the affected vessel appears more pale than the others and the cortex drained by it is pale, surrounded by a zone of light blue staining. After a further five minutes, approximately ten to 20 minutes after the onset, the walls of the affected venule begin to stain an intense blue, many of its continued clumps of red cells remaining a contrasting red color. In this condition no further change occurs within the next four to six hours.

We interpret these changes to mean that the focus of microstasis in the cortical capillary net is associated with engorgement and capillary damage in a number of emerging veins related to the focus, followed by edema from seepage of fluid from the vessels into the surrounding tissue. In the most affected veins this is asso-



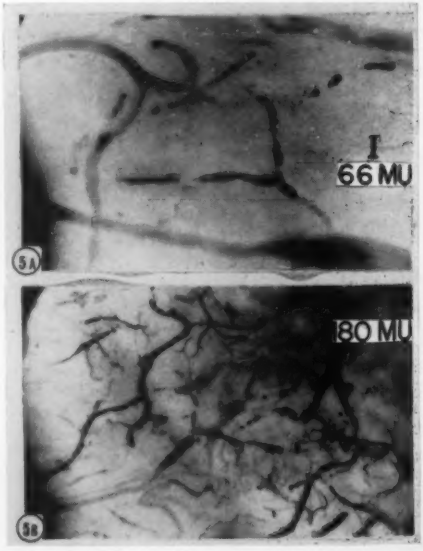


FIG. 4. Series of five photomicrographs of postcentral gyrus (near EPG 1 on diagram) to show changes in cortical vessels. At right of photographs are EPG measurements. Electrode positions are shown in diagram. Blood pressures are noted on each photograph. *A*, photomicrograph during air breathing. B, after 20 seconds of 100 per cent nitrogen breathing, large artery has dilated. *C*, after rupture of middle cerebral artery and lowering blood pressure, stasis appeared in the terminal venuls (arrows). *D*, stasis appeared in arteries (arrows) and veins. *E*, after raising blood pressure with adrenalin, blood flow was restored. EPG units to the right of photographs are x 10^{-8} amps.

FIG. 5. Two photomicrographs taken of the exposed cerebral cortex of the monkey during life to show details of vascular changes in a region of hemorrhagic infarction caused by occlusion of the middle cerebral artery for one hour. *A*, high power view showing stasis in terminal veins and capillaries. *B*, low power view to show perivenous hemorrhages at the border of the infarct, with intact blood flow to the left of the infarcted zone.

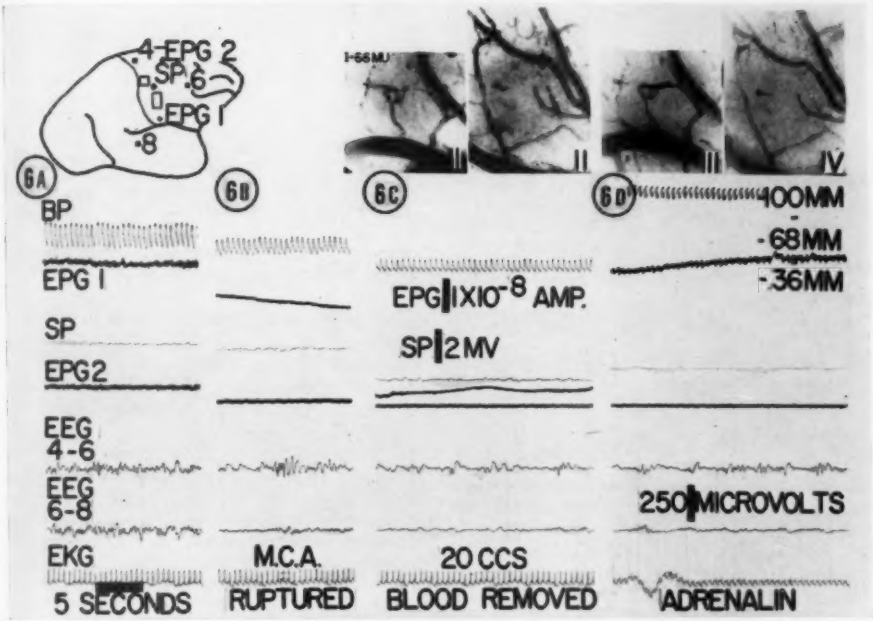


FIG. 6. Four strips of record and correlated photomicrographs of postcentral gyrus to show partial reversal of anemic infarction caused by rupture of the middle cerebral artery. *A*, polygraph prior to rupture of vessel. *B*, 25 seconds after rupture, the EPG oxygen of the Sylvian area is decreasing (EPG 1) and the local electrocorticographic activity is diminished. *C*, 15 minutes after 20 cc. of blood have been removed, an injury potential has occurred with stasis of the pial vessels. (Microphotographs I, II were taken at this point. I shows a meningeal capillary in the whole course from artery below to vein right). *D*, after raising blood pressure with adrenalin, the SP is partially reversed and blood flow is improved in small vessels (III, IV). The Sylvian EPG oxygen returns to normal.

Electrode positions are shown on brain diagram. Time calibration at base of record *A*, EPG and SP calibration on record *C*, electrocorticographic and BP calibrations on record *D*.

ciated with complete stasis and cessation of circulation, with packing and sludging of red cells, followed by necrosis and dark staining of the wall of this vessel.

Hemorrhagic Infarction

In vessels showing complete stasis, perivascular staining with trypan blue did not occur, some degree of blood flow apparently being necessary for this effect. In four experiments diapedesis of red blood cells through the walls of small veins resulted in varying degrees of perivenous hemorrhagic infarction (figures 5 and 7). Flame-shaped hemorrhages around veins are seen occasionally. This phenomenon was particularly striking in the experiment illustrated in figure 1, where the blood pressure was restored following prolonged ischemia and resulted in patchy hemorrhagic infarction. The speed of propagation of these vascular phenomena is related to the effectiveness of the collateral circulation, and the vascular damage appears to be mediated by local ischemic anoxia. Severe local ischemia due to a poor collateral circulation regularly resulted in endothelial damage and stasis appearing within minutes, which may be followed by a macroscopic infarct within an hour. Even when stasis became very extensive as a result of prolonged severe ischemia, thrombosis of arteries did not occur and stasis in arteries was limited to very small vessels. In other experiments where the collateral circulation was well maintained, patchy infarction of the terminal veins was the only vascular lesion noted after six to eight hours of observation.

Relation of Neuronal and Vascular Damage to Localized Anoxia

The rapidity of development of both neuronal and vascular damage and its close relation to reduction in local oxygen tension, as indicated by the EPG electrodes, suggested that they are concomitant results of local tissue an-

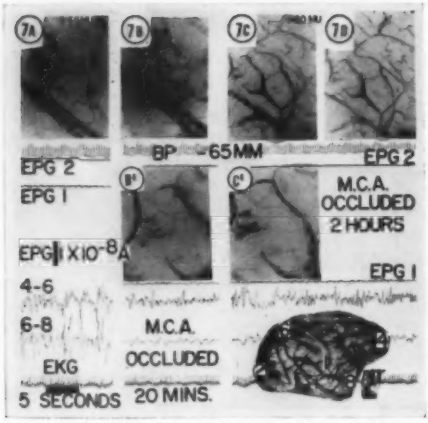
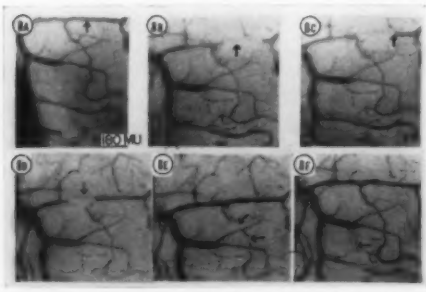


FIG. 7. Three strips of record and correlated photomicrographs of angular gyrus to show infarction caused by occlusion of the middle cerebral artery. *A*, photomicrograph before occlusion. Record below shows corresponding EPG oxygen, blood pressure (BP), electrocorticogram, and electrocardiogram. *B*, photomicrograph (same area) 20 minutes after occlusion to show terminal venous stasis. Record below shows reduced local oxygen in adjacent area and stasis in another vein. (B^1). *C*, Photomicrograph two hours later showing extensive venous stasis. In C^1 there is progression of stasis photographed in B^1. Record of electrocorticogram and EPG oxygen tension unchanged. *D*, photomicrograph to show arterial stasis accompanying terminal circulatory failure. Lower right photograph is of brain at necropsy after right carotid artery was injected with India ink. The vessels did not fill in zone of infarct marked 1 (EPG 1). 2 = EPG 2. 4, 6, 8 = E.E.G. electrodes. Calibrations of EPG, time, and BP are noted on record.

oxia. The threshold for neuronal damage is difficult to compare with that of vascular damage for, other than segmentation and clumping, there is no test of reversible endothelial damage that can be compared directly with the SP change of nerve cells. If occasionally we observed perivenous staining with trypan blue in the absence of SP change, this could be related to the relatively large size of the SP electrode or its position relative to the small areas of microstasis. That anoxia is primarily the cause of microstasis is strongly suggested by its origin on the venous side of the cortical capillary network, and this concept is further supported by microscopic observation of the cerebral vessels during 100 per cent nitrogen breathing. Trypan blue was administered intravenously for purposes of comparison with the occlusion experiments. Nitrogen breathing produced punctate microstasis identical with that described above after as brief a period as 45 seconds of anoxia (figure 9A). The injury consisted of blue staining of capillary walls, followed by terminal stasis. This phenomenon was extended further by occlusion of the carotid arteries (figure 9B and C).

Embolization

In three experiments small microemboli were seen to lodge in cortical vessels following pro-



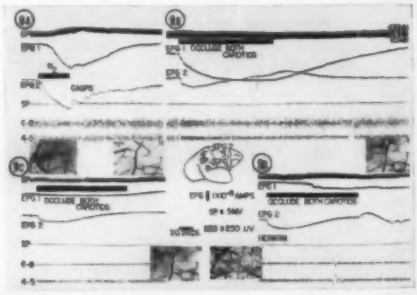


FIG. 8. A series of rapid photomicrographs to show cortical embolization from a fragment of clot after intermittent traction on the middle cerebral artery. *A*, arrow indicates cortical arteriole prior to embolization. *B*, arrow indicates embolus in vessel with terminal venous stasis in the territory of the occluded vessel. *C*, arrow indicates progression of clot one minute later. *D*, arrow indicates further progression two minutes later. *E*, arrows indicate fragments of embolus three minutes later. *F*, photomicrographs five minutes after all emboli have disappeared. Arrow indicates return of segmental blood flow to the areas of stasis.

FIG. 9. Four samples of records and correlated photomicrographs of the postcentral gyrus (near the point marked S.P.) from the same experiment to show terminal venous stasis produced by breathing 100 per cent nitrogen and increased by occlusion of the carotid arteries. *A*. Breathing 100 per cent nitrogen for 45 seconds produced reduction in EPG oxygen (EPG 1 and 2) and terminal venous stasis. Photo I was taken prior to nitrogen breathing and photo II one minute afterwards. The little branched vessel in the upper right of II has both branches in stasis. The same vessel is seen in the upper right hand corner of I at lower magnification. *B*. Occlusion of both carotid arteries caused hypoxia in region of EPG 1 and increase in the stasis (Photo V). *C*. Repeated occlusoin of carotid arteries reduced the amplitude of the electrocorticogram and increased the stasis (Photo III). Note failure of fall in EPG 1 trace in the absence of electrocorticographic activity. *D*. After heparin and partial restoration of the EEG carotid occlusion fails to increase stasis (IV) and EPG 1 trace now shows a small fall.

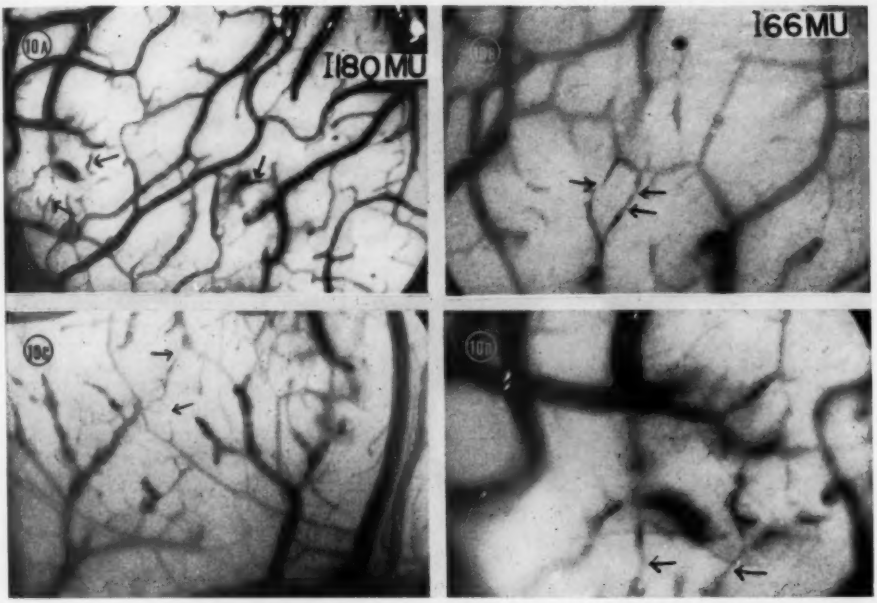


FIG. 10. Four microphotographs of pial vessels to show vascular damage in an area of terminal venous stasis (see text) after the intravenous injection of trypan blue. An orange filter was used. *A*, Low power. Arrows indicate blue staining of walls of venules in areas of microstasis with perivascular staining of larger tributaries. *B*, High power. Arrows indicate areas of clumped red cells (pale due to orange filter) between blue staining venules. *C*, Low power. Arrows indicate areas of stasis surrounded by vessels from which dye is staining the tissue. *D*, High power. Arrows indicate vessels in stasis around which perivascular staining has occurred.

longed occlusion and release of the middle cerebral artery. They were presumed to be small fragments of thrombus that had become dislodged from this vessel and carried by the restored flow of blood to the pial arterioles. These emboli consisted of greyish-white material and lodged temporarily in arteries of 50 to 150 micra in diameter. They were not associated with spasm of the arterial walls at the site of lodgement. After arriving in a cortical arteriole, they gradually moved toward terminal ramifications and in a matter of two to four minutes they began to fragment into minute particles and disappeared into tiny arterioles entering the cortex. Immediately after the arrival of the embolus, as in figure 8B, stasis appeared in the terminal venules of the vascular net supplied by the involved vessel. A few minutes after the embolus had fragmented and disappeared, an irregular slow movement of clumps of sludged blood resumed in some of the areas of stasis (figure 8F).

For purposes of comparison in two experiments 0.5 cc. of air was injected into the carotid artery while observing the cortex for the effects of air emboli. The arrival of the air bubbles was associated with some degree of arterial spasm, but after four minutes they were gradually propelled into the terminal vascular net where they broke up into tiny bubbles and disappeared below the cortex. Here also one or more surrounding venules showed microstasis within the next five minutes.

These microemboli are associated with a local cortical hypoxia, as recorded by adjacent EPG electrodes, and the injection of trypan blue revealed endothelial damage in adjacent venules, with extravasation of the dye outside the walls of those terminal veins where flow had resumed.

Histologic Correlation

In three experiments sections of the exact areas observed for six to eight hours in situ were prepared and examined after suitable fixation and staining. Marked capillary stasis was evident. The experiments were too short in duration for clear histologic change in endothelium to be evident. The subcortical white

matter, as well as the cortex, was found to be the site of extensive histologic abnormality. The cortical neurons and their nuclei were swollen and pale-staining in Nissl preparations and appeared eosinophilic when stained with hematoxylin and eosin. The cortex and subcortical white matter were invaded by polymorphonuclear leukocytes in a patchy manner, and the walls of many cortical and subcortical arterioles and venules were filled with polymorphonuclear leukocytes and surrounded by plasma cells. The endothelial nuceli of many of these small vessels were swollen and occasionally fragmented. The myelin of the subcortical white matter showed beading, irregular swelling, and separation of the fibers. The stroma of both cortex and white matter showed an abnormal looseness and separation. Oligodendroglial and astrocyte nuclei were swollen.

In one experiment when venous thrombosis of unknown origin occurred, possibly because this animal had been debilitated by dysentery, white thrombi were clearly visible in cortical veins and unlike any of the phenomena associated with ischemia and anoxia. Microscopic sections of such thrombi showed the usual composition of fibrin and platelets. These were also seen in emboli derived from damaged carotid or middle cerebral artery.

Effect of Heparin in Experimental Infarction

In the short period of examination of these experiments (eight hours), the injection of heparin (10 mg.) alone did not reverse stasis once it had occurred. Heparin together with a rise in blood pressure was effective in reversing early stasis but, since a rise in blood pressure alone also caused reversal, any beneficial effect of heparin alone was difficult to evaluate. After heparin had been administered the threshold for increasing the degree of stasis by repeated nitrogen breathing and vascular occlusion was raised. For example, in figure 9A, B, and C, progressive stasis was induced by nitrogen breathing and carotid occlusion, but after the administration of heparin occlusion of both carotids did not significantly increase the stasis.

Cerebral Metabolic Rate and Ischemic Neuronal Injury

Areas of cortex that are injured by ischemia with a resultant suppression of the electrocorticogram appear to have a reduced local metabolic consumption of oxygen. For example, in figure 9B, occlusion of both carotid arteries in the presence of a normal electrocorticogram resulted in a steep gradient of fall in the oxygen availability of the Sylvian region (EPG 1) and a delayed rise in the oxygen availability of the bordering zone in the distribution of the anterior cerebral artery (EPG 2). In figure 9C, after repeated occlusion of the carotid arteries the electrocorticogram showed suppression in the Sylvian region (6 to 8) and less marked suppression in the bordering zone (4 to 5). Bilateral carotid occlusion in the absence of electrocorticographic activity produced a minimal fall of the oxygen availability in the injured zone (EPG 1). In figure 9D, 30 minutes later, after heparin had been administered, the electrocorticogram showed a partial return of electrical activity in the Sylvian region. Bilateral carotid occlusion in the presence of an improved electrocorticogram now produced a greater fall in the oxygen availability in the Sylvian region (EPG 1), although not as great as prior to the cortical injury. The pattern of rise in the bordering electrode (EPG 2) was not significantly altered. We interpret the lesser extent of fall in EPG tracing in C and D as the result of reduced tissue demand for oxygen, compared with A and B.

DISCUSSION

Occlusion or rupture of the middle cerebral artery in the presence of a low blood pressure regularly produces neuronal and vascular damage. The severity of damage varies directly with the effective collateral circulation, which in turn is dependent on the level of the systemic blood pressure. Varying the duration of occlusion and manipulating the blood pressure permits the production of different degrees of injury. Brief ischemia results in neuronal paralysis alone that is reversible if the local blood flow is restored by release of the occluded vessel or by increasing the collateral blood flow. Ischemic neuronal paralysis due to localized hypoxia is associated with suppression of the electrocorticogram and development of an injury potential and, if prolonged, results in a decreased tissue demand for oxygen. With restoration of blood flow and the return of neuronal activity, the local oxygen metabolism returns to the steady state.

Vascular damage is an associated effect of ischemic anoxia and appears to have a slightly higher threshold than neuronal damage for some types of anoxia. This is presumed to be due to the higher metabolic rate of nerve cells compared to that of endothelium. The association is a close one and repeated anoxia is soon associated with damage to both vascular endothelium and nerve cells. Thus, a critically reduced blood supply may maintain normal

function of the vascular endothelium but result in paralysis of nerve cells. Once neuronal paralysis has occurred, however, the metabolic need of oxygen is reduced to approximately 20 per cent of normal, this being the basal requirement necessary to maintain the viability of the paralyzed nerve cell.[1,12,13] We have succeeded in producing temporary ischemic neuronal damage in the absence of vascular injury with complete recovery of the electrocorticogram and S.P., although these criteria do not exclude irreversible damage to a few nerve cells. It is unknown how long nerve cells may remain in this state of neuronal paralysis and recover, but clinical observations suggest that functional recovery may be restored after several weeks.

Anoxic anoxia produced by breathing 100 per cent nitrogen for 50 seconds or longer also results in microstasis in terminal venules and an increased permeability to trypan blue of related vessels. This is considered to be critical evidence that the vascular damage caused by ischemia is mediated by anoxia. The usual sequence of events following occlusion of the middle cerebral artery in the monkey is a combination of varying degrees of neuronal and vascular damage. Microscopic inspection of the cortex during both anoxic and ischemic anoxia revealed that both were associated with punctate stasis in the venous side of the capillary net, resulting in microstasis of isolated merging venules. Severe or repeated insult results in the appearance of additional foci and extension of the original ones. The condition is reversible by raising systolic pressure within 15 to 30 minutes of its causation; otherwise it results in punctate infarction. Even when severe this phenomenon is irregular and patchy, since islands of cortex remain relatively preserved in zones surrounding the larger collateral vessels. Continued ischemia results in enlargement of the multiple areas of damage until eventually they coalesce. Only with catastrophic total collapse of the cerebral circulation does a completely pale infarct with segmentation of blood in collapsed vessels occur.

In the early phases the pattern of vascular damage is highly consistent. A sluggish flow of dark blood is seen in isolated terminal venules emerging from the cortex, clumping then occurs, and the walls of the affected venules and capillaries stain darkly with trypan blue, followed by increased permeability of the neighboring small vessels which become surrounded by a spreading blue staining of the tissues. When the damage is severe and confluent there is some degree of extravasated red blood cells and occasionally frank hemorrhage from the most congested venules. It is apparent from microscopic observations that the extravasation of dye and red blood cells requires blood flow to be present within the damaged vessels, and the extent of extravasation appears to depend on the restoration of the local head of pressure in vessels already damaged by ischemic anoxia. For example, hemorrhagic infarction occurred only in those experiments in which an effective collateral blood flow with high systolic pressure was suddenly restored to areas of ischemic damage. Histologic examination of sections of tissue from the same area studied in vitro indicates that a similar process is occurring in the subcortical regions.

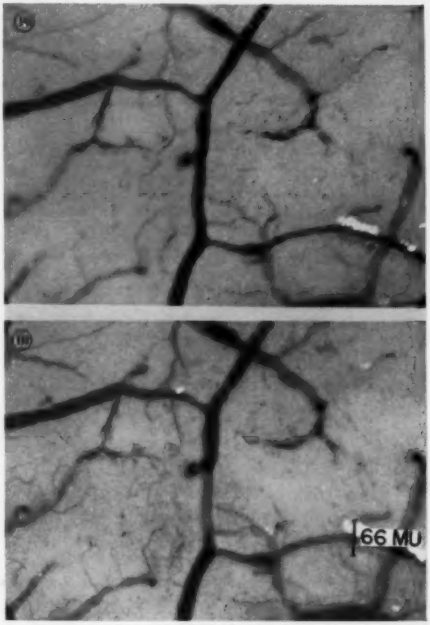


FIG. 11. To show detail of terminal venous stasis. *A*, Enlargement of photomicrograph II of figure 9 showing stasis produced by 100 per cent nitrogen breathing. *B*, Enlargement of photomicrograph V of figure 9 showing increase in stasis by occlusion of both carotid arteries.

Agents which tend to promote the collateral blood flow and prevent local anoxia interrupt the progression of the infarct and in its early stages may reverse the process. The beneficial effects of such measures as breathing 100 per cent oxygen, raising the blood pressure, and restoration of blood flow within the occluded

vessel can readily be seen. Heparin appears to prevent further extension of the process, but within the time limits (eight hours) of these experiments it has reversed early stasis only when there was an associated rise in blood pressure.

The consistent appearance of segmentation and stasis in the terminal venules as the first event following occlusion of a large cerebral vessel appears to be an important clue to the pathogenesis of cerebral infarction. The importance of endothelial damage and stasis in the production of massive infarction has been emphasized in a previous study.[14] In the experiments reported here we have found no evidence that formation of thrombi plays any significant part in the process of ischemic and anoxic infarction produced by these methods. Even when portions of thrombotic embolus lodged in a cortical vessel, the process of microstasis was manifest. It would appear, therefore, that in many of the conditions called "cerebral thrombosis" the primary event is ischemic anoxia leading to patchy, then confluent microstasis of the venous side of the capillary net. From these experiments it is not possible to make any statment regarding the part played by thrombosis after the first few hours.

Capillary stasis due to anoxia has been reported by Landis in the mammalian mesentery.[15] Direct measurement of capillary pressures has shown that under normal conditions hemoconcentration occurs on the venous side of the capillary circulation,[16] which would be increased by a reduced rate of blood flow and increased permeability of the vessel walls. This hemoconcentration presumably results in a local increase in blood viscosity and predisposes this area to stasis. With the added factor of vascular damage, it is not surprising that the process of infarction should begin in the terminal venules. The restoration of local blood flow by way of collaterals in areas of vascular damage results in an increased capillary filtration rate and local brain edema. The extravasation of trypan blue around larger vessels indicates that this increased permeability contributes to local swelling. The histologic appearance of the damaged areas after fixation confirms the observations made in vivo. The blue-staining capillaries are filled with concentrated trypan blue and the nerve cells and myelin are swollen in the area of infarction.

Finally, it should be noted that one of the factors found in our earlier experiments to contribute to successful but delayed compensation by the collateral cerebral vessels was the cerebrovascular resistance of the ischemic area. The microstasis described here would be a potent factor in raising the cerebrovascular resistance in such an area. One of the chief events of a hemodynamic crisis resulting from critical fall of blood pressure in a cortical area compromised by occlusion or stenosis of a large afferent vessel would be the ability of rising collateral supply to overcome increasing vascular resistance due to endothelial damage.

CONCLUSIONS

1. Cortical ischemia can proceed to the point of failure of electrocorticogram, with production of injury potential, yet recover rapidly and apparently completely without evidence of damage to vessels.

2. Prolongation of anoxia beyond this point results in stasis in isolated small venules emerging from cerebral cortex. From observation of meningeal capillaries and from trypan blue studies, it was shown that such venules drain isolated punctate areas in the venous side of the cortical capillary network.

3. Within 15 to 30 minutes of its production, such microstasis is reversible by increase of blood pressure. Heparin appeared to make its production more difficult.

4. Increased severity of anoxic insult increased the number of foci of stasis and the extent of each focus. Confluence of such foci led to infarction.

5. Infarction from anoxia thus appears to result primarily from damage to vascular endothelium with resulting edema, hemoconcentration, sludging, and stasis.

6. Anoxic anoxia has the same effect as ischemic anoxia. The mechanism is common to all types of vascular insufficiency resulting from obstruction at a distance, including embolism.

7. Thrombosis appears to play no part in the early stages of the process of obstruction of cortical vessels in an area of ischemic damage.

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■ A practitioner must not be a pathologist only, although, unless he be a pathologist, he cannot be a good practitioner. Division of labour, strictly or figuratively, is the law of everything whatever. Some of us work chiefly at physiology, some of us at pathology, and some of us at clinical medicine. But to be a good practitioner, a man must know much of all three, and most of us nowadays carry on the three lines of investigation. Every case is a departure from healthy states, and no one is fitted to begin the scientific study of diseased persons unless he know much of the anatomy and physiology of healthy people. To a great extent, diseases are, metaphorically speaking, experiments, anatomical and physiological on the human body. If if be not profane to say so, I would suggest that anatomists and physiologists might have more recourse to these "experiments." Charcot, in doing the best kind of pathological work, has, I should suppose, done as much for the anatomy and physiology of the spinal cord as anyone living. He is clinical all round. The three things make up the clinical problem. I do not mean that we have simply to draw incidently on our anatomical and physiological knowledge when we see a patient, but that anatomy and physiology are integral parts of every case we have to do with.

J. Hughlings Jackson in *Address on Pathology*, published in 1882.

CLINICAL PATHOLOGIC CONFERENCE

E. P. Richardson, Jr., M.D. Section Editor

Presented by *Warren H. Kempinsky, M.D.*, *Irwin Levy, M.D. and Martin Silberberg, M.D.*

CASE PRESENTATION

A 14 year old white girl was well until July 6, 1949. On the morning of that day she was found in bed having a generalized convulsion. She was admitted to St. Louis City Hospital two and one-half hours later.

She had had measles and pertussis and there had been some recent frontal headaches, but the past medical history was not significant otherwise. Before the onset of the present illness, she had been physically active with a satisfactory school record. An uncle had convulsions and mental deficiency.

On admission she was stuporous and speech was thick. This cleared rapidly and the neurologic examination was normal at that time. Blood count, serology, and urinalysis were normal. Cerebrospinal fluid showed an initial pressure of 150 mm. of water, no cells, protein 44 mg. per cent, sugar 18 mg. per cent, and chloride 735 mg. per cent. Spinal fluid Wassermann was negative and the colloidal gold curve normal. Roentgenograms of the skull were normal; an electroencephalogram showed a moderate slow dysrhythmia with a right posterior focal trend.

There were no further seizures and she was discharged three days after admission on Dilantin sodium.

In the year that followed she had eight or ten convulsions, usually occurring early in the morning. She was sometimes difficult to arouse in the morning, even though no convulsion had occurred. Frequently she was confused for the first quarter of an hour after arising. During that year she became irritable, behavior was sometimes erratic, and she fell behind her classmates in school. In April 1950 she was found to have right otitis media and chronic tonsillitis when seen in the outpatient clinic. A small dose of phenobarbital was started and she was changed from Dilantin to Mesantoin, then back to Dilantin, in an attempt to control convulsions and to avoid drowsiness and episodes of irrational behavior.

Two mild seizures occurred during the night of August 29, 1950, after a seizure-free interval of about one month. From then until her second hospital admission, about 36 hours later, her state of consciousness fluctuated between sleep and open-eyed unresponsiveness. She was admitted on August 31.

On examination her pulse was 100 per minute and there were occasional extrasystoles. She lay quietly in bed with eyes wandering aimlessly. She did not respond to questions, but withdrew from painful stimulation. There was splotchy flushing of the face and shoulders.

Total white count was 14,950 per cu. mm., with 91 per cent segmented forms. Urinalysis was normal. Cerebrospinal fluid was examined on September 1 and September 3. The first of these examinations showed an initial pressure of 294 mm. of water, the fluid contained three white blood cells, and protein content was 81 mg. per cent. The initial pressure on the second occasion was 208 mm., and the final pressure was 124 mm. after removal of 10 cc. of fluid. There were no cells and the fluid contained 65 mg. per cent of sugar.

The patient remained in the hospital until the time of her death on March 5, 1951. Throughout this time her state of consciousness was altered, ranging from slight response to questions to complete unresponsiveness to all stimuli. She never spoke and was tube fed. Neurologic status shifted from left hyporeflexia to right hypertonus, to right spastic hemiplegia, to right flaccid hemiplegia. During the period of the right-sided hemiplegia she had a number of left-sided convulsions. She rolled and twisted irregularly in bed, but this stopped by mid-January and thereafter all extremities were flaccid.

There were occasional elevations of temperature before the latter part of January. Fever then became constant and rales were heard in the chest in February. This was followed by the development of decubitus ulcers, cachexia, and anemia.

During the early part of this hospitalization, roentgenograms of the chest, skull, and cervical spine were normal. Chest films in February showed right lower lobe consolidation and patchy infiltration of the lower two-thirds of the left lung field. A third cerebrospinal fluid examination was made on September 20, 1950. The initial pressure was 172 mm., final pressure 102 mm. There were 10 red blood cells per cu. mm.; the fluid contained 36 mg. per cent of protein and 32 mg. per cent of sugar. Leukocytosis was present from time to time, with total white cell counts of 28,100, 9,400, 21,700, and 18,850 from October to February. Segmented forms predominated in these and there was "left-shift" in some of the differential counts. The last cerebrospinal fluid examination was on

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November 6, 1950. The fluid showed an initial pressure of 85 mm.; it contained no cells, the total protein was 168 mg. per cent, and sugar was 16 mg. per cent.

She expired on March 5, 1951.

CLINICAL DISCUSSION

DR. IRWIN LEVY: We are presented initially with the problem of a 14 year old girl who was found having a generalized convulsion. In such a case it should be remembered that idiopathic convulsive disorder may have its onset at puberty; presumably this is related to metabolic changes which occur at that time. The frequency of onset of the idiopathic disorder at this age could throw one off guard so that he might overlook other diagnostic possibilities. This patient had had measles and pertussis; either of these could have been the basis of an encephalitis, which then resulted in a convulsive disorder. There is nothing in the history, however, to suggest that either of these childhood diseases was complicated by encephalitis. The history of convulsions with mental deficiency in an uncle is suggestive of a hereditary background for neurologic disorder in our patient.

The initial laboratory data was normal, with the exception of the cerebrospinal fluid sugar. Assuming that this was not a laboratory error, such a low sugar could relate to one of three possibilities. These are: bacterial meningitis, diffuse neoplasia of the leptomeninges, and hypoglycemia. Hypoglycemia may be the cause because cerebrospinal fluid sugar is directly related to blood sugar, being usually about two-thirds of the value of the latter.

The electroencephalogram on the first admission showed only a focal trend; these are not uncommon with convulsive disorder in children and are not regarded as a basis for air encephalography.

The occurrence of convulsions in the early morning is of little help in deciding the etiology since this may occur either with tumor or with idiopathic convulsive disorder. Similarly, the early morning confusion is not too helpful because petit mal seizures may occur at that time. Also the patient could have had an early morning generalized convulsion followed by postconvulsive mental confusion. It should also be mentioned that hypoglycemia could have accounted for the early morning confusion.

Initially the personality change might have been regarded as the result of uncontrolled convulsions or of an overdose of anticonvulsant drugs. However, the subsequent development of progressive drowsiness and further deterioration became too severe to be regarded simply as a consequence of the usual convulsive disorder.

At the time of the second admission two seizures were followed by a marked change in the state of consciousness. The question arises whether this change could have been the result of the seizures alone. In status epilepticus where there are frequently recurring convulsions without intervening periods of consciousness, a patient may ultimately deteriorate to a decorticate state. These patients show marked disorganization of the electroencephalogram and, in some, there are structural changes in the brain. Occasionally patients remain in a permanent coma following status epilepticus but the electroencephalogram returns to normal. These cases are most likely due to degenerative lesions in the midbrain. In the case at hand there certainly were not enough seizures to be considered status epilepticus, and I do not believe that the sustained alteration of consciousness could have resulted from seizures alone.

There was no evidence of increased intracranial pressure in this patient, with the exception of an elevated cerebrospinal fluid pressure on the first lumbar puncture of the second hospital admission. The protein content was elevated on two occasions during the second admission. On the basis of these findings and the progressive course of the patient, air encephalography was warranted and I understand that this was done. The time that it was performed and the results have not been given to us for this discussion.

Although air encephalography was justifiable, it does seem most likely from the clinical course that this patient had widespread degenerative changes in the central nervous system. The course would have been slow for Schilder's disease; an onset without cerebral blindness would not be classic but, at the same time, would not be incompatible with that diagnosis. Inclusion body encephalitis may run such a protracted course; however, there is usually an early onset of persistent myoclonic seizures.

The physical and radiographic findings in the chest could presumably have been those of a pneumonia secondary to the patient's physical inactivity and aspiration. I wonder if we might have the radiologist's interpretation of the films?

DR. WARREN H. KEMPINSKY: The radiologist's interpretation was pulmonary tuberculosis.

DR. LEVY: In view of this interpretation, we must consider whether tuberculosis could have been responsible for the entire clinical course. Tuberculous meningitis could cause such a low spinal fluid sugar, but the remainder of the course would not permit such a diagnosis. It might also be mentioned that pulmonary and meningoencephalitic sarcoidosis may rarely occur together and low spinal fluid sugar may be part of that picture.

There is one bit of information which is conspicuous by its absence from the protocol; I have avoided asking about it until now. Dr. Kempinsky, what was this patient's blood sugar?

DR. KEMPINSKY: During the entire 20 months of this patient's illness, there was only one blood sugar value recorded in the hospital chart and that was drawn 12 days before death. The blood sugar at that time was 19 mg. per cent.

DR. LEVY: In view of this information, I believe that we need only consider hypoglycemia as the cause for the central nervous system disorder. Considering the persistence and severity of the symptoms and signs, it seems most likely the hypoglycemia must have been due to an islet cell adenoma of the pancreas.

PATHOLOGIC DISCUSSION

DR. MARTIN SILBERBERG: The brain was not remarkable grossly. Microscopic examination disclosed numerous small perivascular hemorrhages, with vacuolation and lysis of neurons scattered diffusely throughout the cortex and the brainstem. Multiple small areas of encephalomalacia containing many lipid-laden "gitter" cells were also found in these locations. Many of these foci showed proliferation of capillaries and newly formed neuroglial fibrils. These latter foci were thus much older than the fresh hemorrhagic lesions. In still other areas of the midbrain and especially of the pons, glial nodules composed essentially of microglial elements were identified.

The changes observed are indistinguishable from those that might result from repeated episodes of severe generalized cerebral anoxia. These episodes must be considered as repeated injuries to the brain because the lesions were

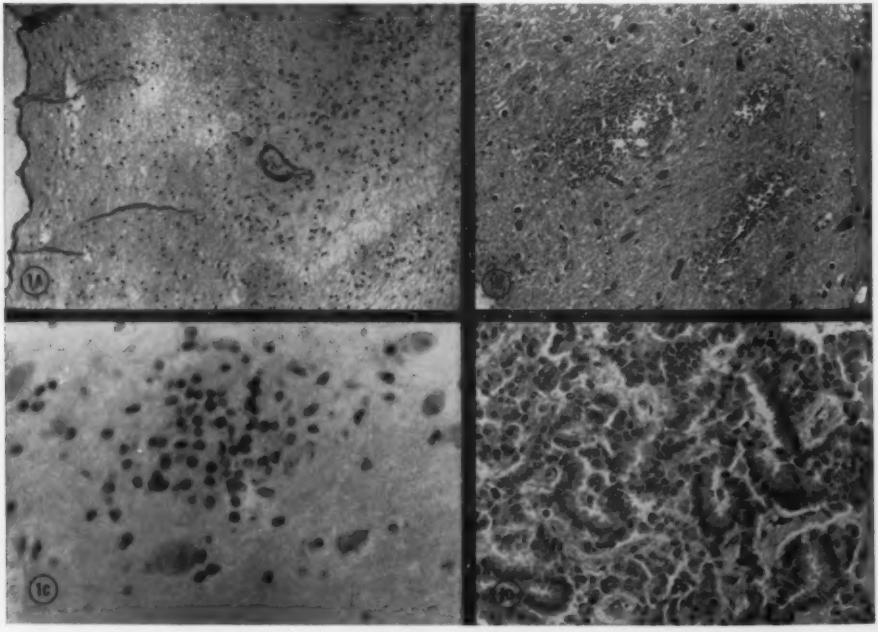

FIG. 1. *A*, periventricular area of encephalomalacia containing lipid-laden "gitter" cells, low power magnification. *B*, microscopic focal hemorrhages, pons, low power. *C*, glial nodule, composed principally of microglial elements, high power. *D*, islet cell adenoma of pancreas, high power.

of a great variety of age, ranging from a few hours to many months or even years.

The lungs showed caseous tuberculosis and there was miliary tuberculosis involving spleen and liver. Acid-fast organisms were shown histologically. The adrenal cortices were hyperplastic.

In the body of the pancreas, two circumscribed greyish pinkish nodules, each measuring about 1 cm. in diameter, were seen. One was located in the head and one in the tail of the pancreas. Microscopically they had the characteristic structure of islet cell adenomas. Such tumors are not rarely multiple. These neoplasms obviously formed the basis of this patient's hypoglycemia.

DR. KEMPINSKY: Dr. Silberberg and I brought this case to light because it illustrated several important facts about hypoglycemia. I would like to say a little more about the cause of the lesions. It has been mentioned a number of times in the literature[1,2] that the cerebral lesions are structurally indistinguishable from those of anoxia. This is well illustrated by the present case. There is good reason for this relationship; I would like to show a slide which illustrates the point (figure 2).* It shows the decline of blood sugar and the simultaneous fall of the cerebral arteriovenous oxygen difference which follow the administration of a sufficient dose of insulin. This data was taken from determinations done on a schizophrenic patient who was undergoing insulin coma therapy. Let us take the liberty of applying this data to our patient. When her cerebrospinal fluid sugar was 16 mg. per cent, her blood sugar would have been approximately

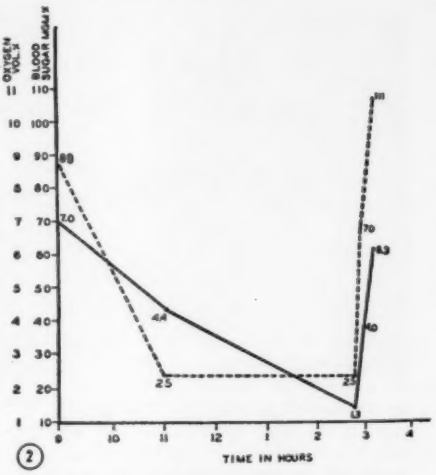

FIG. 2. Relationship between blood sugar and cerebral arteriovenous oxygen difference in hypoglycemia. (Reproduced by courtesy of Dr. Harold E. Himwich and Williams and Wilkins Company.)

23 mg. per cent or very close to that shown in the graph. After some time at this level, her cerebral arteriovenous oxygen difference could have fallen to near this low level of 1.3 volumes per cent. The validity of this measurement as an index of cerebral oxygen consumption is established by the observation that cerebral blood flow is not significantly changed from normal during hypoglycemia.[4] In other words, due to energy lack, the brain was consuming only about 20 per cent of the usual quantity of oxygen. This obviously provided the basis for the development of lesions identical with those of anoxia.

*Figure 1 from Himwich's *Brain Metabolism and Cerebral Disorders.*[3]

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CASE REPORT

Myasthenia Gravis Appearing After the Removal of Thymoma

Lewis P. Rowland, M.D., Henry Aranow, Jr., M.D. and Paul F. A. Hoefer, M.D.*

THE INCIDENCE OF THYMOMA among patients with myasthenia gravis is between 15 and 30 per cent. The lower figure is derived from cases subjected to surgery[1–3] and may be erroneously low, because patients with thymoma are sometimes rejected for surgery and because the tumor may not be discovered during life. The greater incidence has been found in autopsy series[4,5] and may be erroneously high if, as has been suggested by several authors, the tumor is associated with a more malignant form of myasthenia than encountered in patients who have no tumor.

On the other hand, a large proportion of patients with thymoma also have myasthenia gravis. At the Mayo Clinic, of 45 patients with thymoma, 34 also had myasthenia gravis[6] and more recently Gray[7] has reported that the incidence has not changed. At the Columbia-Presbyterian Medical Center 11 of 33 thymomas have occurred in patients with myasthenia,[8] and a similar incidence was found among 32 thymomas studied at the Armed Forces Institute of Pathology and the University of Michigan.[9] There seems to be little doubt that there is a significant relationship between myasthenia and thymoma, but the nature of this association has not been elucidated. The question may be raised whether thymic abnormality causes myasthenia in some manner. The best evidence for this hypothesis is that thymectomy often has a beneficial effect on the disease,[1–3] and Wilson[10] has recently reported the presence of a neuromuscular blocking substance in extracts of thymic tissue removed from myasthenic patients. Iverson[11] believes that the epithelial cells of thymomas in patients with myasthenia resemble secretory endocrine cells, whereas thymomas from nonmyasthenic patients do not have this apearance.

There are, however, several facts which cast doubt on the hypothesis that thymic abnormality causes myasthenia: 1) myasthenia may occur in the absence of any anatomic abnormality, or indeed in the absence of any discernible thymic tissue;[5] 2) the results of thymectomy are unpredictable in any given case and, at the hospital in which the procedure was originally advocated, the operation has been largely abandoned;[12] 3) when improvement does follow thymectomy, there may be subsequent relapse without evidence of recurrence of the tumor;[2] 4) the results of thymectomy are reported to be better for patients who have no tumor than for those who do;[1–3] 5) there is no correlation between the size or cellularity of the thymoma and the severity of myasthenia;[13] 6) there may be complete remission of myasthenia despite the presence of a thymoma;[5] 7) in attempting to reproduce Wilson's demonstration of a neuromuscular blocking substance in thymic extracts, Zacks and Cohen[14] have found that the toxic properties may be due to the potassium-content of the material rather than to a truly curariform substance; 8) myasthenia may appear for the first time after removal of a thymoma.

The present study is devoted to a consideration of the last problem. We are aware of ten cases in which myasthenia has appeared after the removal of thymoma and these are summarized in table 1. Of these, five case reports have been published by others,[15–19] two are in the process of publication,[20,21] and two of the cases to be described here have previously been mentioned by us[5,22,23] but not presented in detail. The last case has not been described previously. In addition to these cases, others

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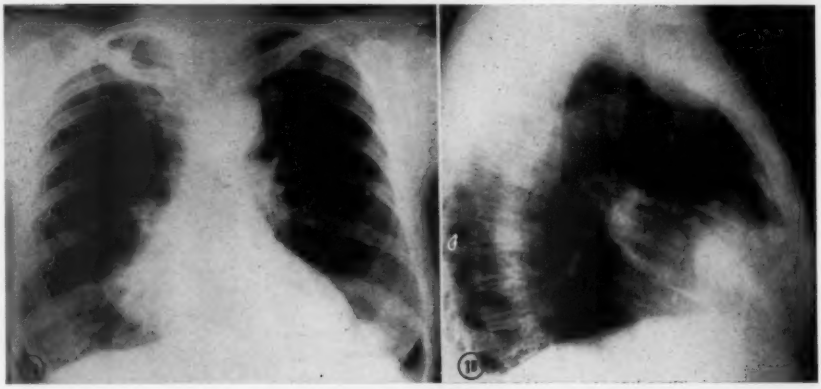

FIG. 1. (*Case 3*). Preoperative roentgenograms demonstrating thymoma in anterior mediastinum.

have been mentioned[7,24] but without detail.

CASE REPORTS

Case 1. A 50 year old woman was admitted to the Neurological Institute on July 6, 1951. In 1946 she had been admitted to another hospital because of a cough of a few days duration but she was otherwise asymptomatic. An anterior mediastinal mass was seen in a chest film and upon surgical removal this proved to be a thymoma. She was then well until June 1951 when she developed ptosis, dysarthria, dysphagia, and dyspnea. There was no roentgenographic evidence of thymoma. A neostigmine test was positive and she was treated with this drug. On July 11 she had an episode of sudden respiratory distress which was relieved by parenteral neostigmine, tracheal suction, and artificial respiration for 30 minutes. During the next few days she seemed

TABLE 1

SUMMARY OF CASE REPORTS OF PATIENTS WHO DEVELOPED MYASTHENIA GRAVIS SUBSEQUENT TO THE REMOVAL OF A THYMOMA

Case	*Author*	*Sex*	*Age at Time of Surgery*	*Tumor Completely Removed*	*Interval Before Appearance of Myasthenia Gravis*	*Outcome*	*Autopsy*
1	Fehrstand & Shaw[15]	M	27	No	Immediate	Died four months postoperatively	Residual invasive tumor
2	Present series[22,23] (case 1)	F	46	Yes(?)	4½ years	Died one month after onset of myasthenia gravis	No
3	Mendelow & Genkins[17] (case 4)	F	37	No	1 month	Duration not stated	Residual invasive tumor
4	Fisher & Child[16]	M	51	No	Immediate	Died four days postoperatively	No
5	Strieder[19]	—	—	—	2 years	One year after appearance of myasthenia gravis, "complete thymectomy" followed by remission for two years	——
6	Ringertz & Lindholm[4]	M	20	Uncertain	2 years	Appearance of myasthenia gravis associated with outgrowth of pleural metastasis which were removed. Patient died four years after original thymectomy	Local recurrence of tumor and hyperplastic thymus
7	Madonick et al.[20]	F	32	Yes	3 years	Patient still alive; re-exploration showed some thymic tissue but no tumor	——
8	Present series[5] (case 2)	M	56	Yes	2 weeks	Died 1½ years later	No residual tumor but some hyperplastic thymus
9	Present series (case 3)	F	73	Yes	18 months	Died 6 months after onset of myasthenia gravis	No
10	Stone[21]	M	45	Yes	20 days	Patient alive 3½ months after onset of myasthenia gravis	——

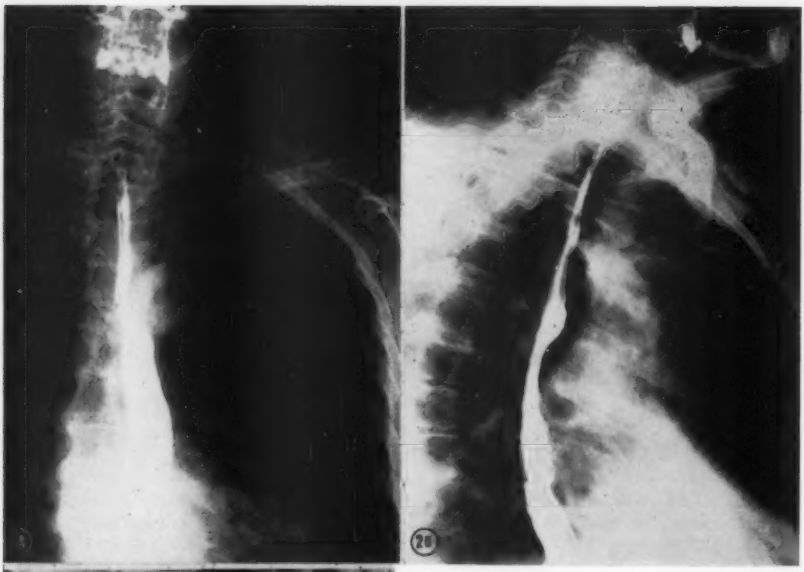

FIG. 2. Postoperative esophagrams (*A* and *B*) taken 18 months and ten months, respectively, prior to the onset of symptomatic dysphagia. Retention of barium in the pyriform sinuses and valleculae is evident and suggests impairment of the swallowing mechanism. A similar defect (*C*) was demonstrable after myasthenic symptoms became overt.

to be doing well, but on July 16 she had another sudden episode of respiratory distress and died. Permission for postmortem examination was not obtained.

Case 2. A 56 year old man was found to have an anterior mediastinal mass on a routine chest film in 1951. He was asymptomatic and thoracotomy was deferred. During the next two years the tumor was seen to grow larger and became calcified. In 1953 he began to complain of exertional dyspnea, hoarseness, and cough. On May 6, 1953 a thoracotomy was done elsewhere. There was a well-circumscribed mass in the anterior mediastinum which was attached to the right lung at one site, but which was removed completely and proved to be a thymoma. He felt well postoperatively, but shortly after going home he had to support his head while sitting erect because of cervical weakness. This disappeared after a week or two. In January 1954 he began to have dysphagia and dysarthria. In March weakness of the extremities ensued and improved after the administration of neostigmine. He was admitted to the Neurological Institute on July 8, 1954, where neurologic examination was normal except for rapid fatigue of the arms, hands, and eyelids. He was discharged on July 16. He was subsequently treated with pyridostigmine (Mestinon), but, although he improved initially, he was taking 240 mg. every two hours by September 13. Dyspnea at rest occurred and became severe on September 24, 1954. He was given parenteral neostigmine at home and was rushed to the hospital, but was dead upon arrival.

Postmortem examination. There was no evidence of tumor, and grossly there was no tissue which could be certainly identified as thymus,

but some questionable areas of anterior mediastinal tissue proved to be hyperplastic thymus on microscopic examination.

Case 3. A 73 year old woman became dyspneic but had no other symptoms in April 1953. On roentgenograms a mass was seen in the right chest (figure 1) which, after total removal, proved to be a thymoma. Her postoperative course was benign and she remained well until August 1955, when she began to have ptosis of the eyelids and diplopia, which fluctuated in severity. In October she began to have dysarthria and dysphagia.

She was admitted to Montefiore Hospital on December 14, 1955. Her ocular palsies and ptosis responded dramatically to edrophonium chloride (Tensilon), 10 mg. intravenously. Tomography of the mediastinum revealed no evidence of residual tumor. She was subsequently treated with neostigmine, pyridostigmine, and ambenonium in various combinations, but died on February 6, 1956. Autopsy was not permitted.

DISCUSSION

If myasthenia gravis develops after the removal of a thymoma, it seems unlikely that the tumor can be causing the muscular weakness. On the basis of the information available in the ten cases reported, however, the possibility that thymic influences cause myasthenia is not completely excluded, for the following reasons:

1. Of the ten cases, myasthenia appeared at the time of surgery in two (cases 1 and 4, table 1), and in one of these operations curare was used to secure muscular relaxation. It is possible that mild unrecognized evidence of myasthenia had been present preoperatively in these cases and perhaps in three others (cases 3, 8, and 10, table 1) in whom the myasthenia definitely appeared within one month of the operation.

2. Even in the five cases in which thymectomy preceded the myasthenia by an asymptomatic interval of more than one year (cases 2, 5, 6, 7, 9, table 1) it is possible that "subclinical" myasthenia was present preoperatively. That this may be so is suggested by the postoperative films of case 3 of the present series (figure 2). Although these films were taken 18 months and ten months prior to the onset of symptomatic dysphagia, they show retention of barium in the pyriform fossae and valleculae, described originally by Schwab and Viets[28] as being indicative of pharyngeal weakness in myasthenia gravis.

3. In none of these ten cases can it be stated definitely that there was no residual thymus. In three cases (cases 1, 3, and 4, table 1) the tumor could not be completely removed because of invasion of adjacent structures. In one case (case 8, table 1) the tumor was completely removed, but at autopsy there was hyperplasia of some thymic remnants. In the cases of Madonick and co-workers,[20] Strieder,[19] and Ringertz and Lindholm,[18] re-exploration of the mediastinum revealed residual thymic tissue. There has been no anatomic examination of the mediastinum in the other three cases.

Nevertheless, these cases make it seem unlikely that the thymic tumor itself bears a causal relationship to myasthenia gravis. Of the alternative explanations for the association of these two conditions, it seems unlikely that myasthenia causes the thymoma. The remaining possibility is that both the thymoma (or other thymic abnormality) and the myasthenia are the result of a common etiologic factor.[25] If this is so, the nature of that factor is not known and clinical improvement after thymectomy remains unexplained.

It is possible that the effect of thymectomy is not specific but that the responses of the body to any major stress are such that myasthenia is also affected favorably. This may be the explanation for the striking remissions which are not infrequently seen after recovery from a myasthenic crisis and the improvement which is reported to follow such nonspecific operations as carotid sinus denervation,[29,30] excision of an echinococcus cyst of the lung,[27] or mediastinal exploration without removal of any thymic tissue at all.[12] In our own series of more than 200 cases of myasthenia gravis, major surgical procedures have not been sufficiently frequent to provide direct evidence of this possibility.

SUMMARY

Case reports of three patients are presented in whom myasthenia gravis appeared after the removal of a thymoma. Analysis of the clinical and pathologic features of these cases and seven similar cases reported from other centers makes it seem unlikely that the thymic tumor causes the myasthenia, but they do not completely exclude the possibility that some thymic abnormality is responsible. It seems more likely that both the histologic changes in the thymus and myasthenia gravis result from a common cause.

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■ With respect to the uses of the nervous system, Drs. Gall and Spurzheim entertain some opinions materially different from those of the generality of modern physiologists. In man, and the more perfect animals, the manifestations of all the faculties, they allow, "are more or less subordinate to the influence of the nervous system. Besides the functions of the five external senses, all the instincts, propensities, sentiments and intellectual faculties, all affections and passions, all the characteristics of humanity, are manifested only by means of the nervous system." But they maintain that all the functions of the animal as well as of the automatic life are *innate*, and in proof of this they allege "the constancy of the human character; the uniformity of the nature of man at all times, and in all countries; the tendency of natural genius; the determinate character of each of the sexes; the peculiarities of every individual; the relation between the organization and the manifestations of the respective faculties; and the circumstance that man is a created being."

John Cook in *A Treatise on Nervous Diseases*, published in 1824.

CASE REPORT

Oligodendrogliomatosis With Intracranial Hypertension

Julius Korein, M.D., Irwin Feigin, M.D. and Mortimer F. Shapiro, M.D.*

FROM A CLINICAL VIEWPOINT, the oligodendroglioma is not usually considered to be a metastasizing neoplasm. However, its spread through the spinal fluid along the ventricular and leptomeningeal spaces has been observed in a small number of cases.[1,2] Earnest, Kernohan, and Craig,[3] in a review of 165 cases of oligodendroglioma, reported that seeding of the tumor via the cerebrospinal fluid was noted in 14 patients, or 8 per cent of the series. Beck and Russell[4] described four such cases in detail and introduced the term oligodendrogliomatosis.

Widespread involvement of the meninges by gliomatous tumors, for which the term "meningeal gliomatosis" has been used, is rare.[5] Statistically, of those gliomas that behave in this fashion, the oligodendroglioma constitutes a small percentage. In Polmeteer and Kernohan's discussion of 42 cases of meningeal gliomatosis, the neoplasm was an oligodendroglioma in only five, or about 12 per cent.[6]

The case of oligodendroglioma to be described below is one of diffuse involvement of the leptomeninges. It is of interest because of its rarity and its unusual clinical course.

CASE REPORT

The patient first entered Mount Sinai Hospital in May 1953 at the age of 16 for evaluation of his petit mal seizures and the relationship of these seizures to a pattern of chronic and episodic behavior disturbance.

The patient was born after a normal gestation period and an uneventful delivery. He developed normally until the age of two, when he began to have episodes of cyanosis and emesis, followed by sleep. These episodes ceased after tonsillectomy. When he was seven, the patient began to have seizures which were characterized by sudden cessation of speech and motor activity, followed by stiffening of the left arm and leg. After a few seconds he would resume normal activity. A diagnosis of petit mal was made. He was treated with anticonvulsant drugs and some decrease in frequency of the seizures was noted. At the age of ten years he had an isolated grand mal seizure. His behavior became asocial and was marked by sudden, apparently uncontrollable rages and severe mood swings. Because of these disturbances he was temporarily institutionalized at Bellevue Medical Center at the age af 11. Despite all this, the patient's intelligence appeared to be superior. He completed high school at the age of 16. Psychologic tests revealed an IQ (Wechsler-Bellevue) of about 130.

When he was first admitted to Mount Sinai Hospital detailed neurologic examination disclosed bilateral papilledema, nystagmus on lateral and upward gaze, and some diminution in visual acuity. The cerebrospinal fluid was under a pressure of 500 mm. of water but had a protein content of only 54 mg. per cent. An electroencephalogram revealed focal slowing and spiking over the right temporal region. Roentgenograms of the skull including tomograms (figure 1) showed calcification in the right temporal lobe, to the right of and superior to the sella. Angiography was attempted but was unsuccessful. A ventriculogram demonstrated normal sized, undistorted ventricles. There was no shift of the third ventricle.

Despite the fact that there was no compression of the ventricular system, a presumptive diagnosis of cerebral neoplasm was made. Accordingly, an exploration of the right temporal lobe was performed. It was noted that a large amount of cerebrospinal fluid escaped when the dura was incised and that the previously bulging brain slowly receded. Nothing abnormal was found on the surface of the temporal lobe which was explored toward the base and anteriorly. The opinion at the time of surgery was that the pathology was not that of an expanding mass, but rather that of an abnormally increased amount of cerebrospinal fluid, so-called "serous meningitis." The calcification in the right temporal lobe was considered to be congenital, probably a sequel to birth trauma. The skull was closed leaving a right myeloplastic decompression.

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FIG. 1. Tomogram of skull demonstrating suprasellar calcification.
FIG. 2. Pneumoencephalogram demonstrating shift of dilated ventricular system to the right.

The papilledema receded and the patient was discharged to be followed in the neurology clinic. He was given a variety of anticonvulsant medications, but frequent petit mal seizures and the behavior disturbance continued.

Within a year he began to develop frequent grand mal seizures. These were preceded by a sensory aura in the left hand and it became necessary to hospitalize him three times in April, May, and June 1954. During these admissions the clinical picture, as summarized below, was essentially the same.

The right temporal decompression site was bulging but not tense. Nystagmus persisted in all directions of gaze and he still had bilateral papilledema. The spinal fluid was clear and colorless, with a normal number of cells, but the initial pressures showed a progressive increase from 180 to 200 to 230 mm. of water. The protein values were also elevated at this time — 120, 137, 114 mg. per cent, respectively. The electroencephalogram was persistently abnormal, with focal slowing over the right midtemporal area.

A pneumoencephalogram in June 1954 (figure 2) showed marked dilation of the right lateral and third ventricles. The third ventricle, especially in its upper portion, was shifted to the right. The right temporal horn was markedly dilated and deviated toward the bulge at the decompression site.

During each of these admissions it was noted that there was an abrupt cessation of the grand mal seizures and that his behavior on the ward was quiet and cooperative. It was believed that emotional elements may have played some role in triggering the seizures.

He returned for his fifth and final admission in September 1954, because of the development of left hemiparesis, diplopia, and pain around the right orbit. Repeated grand mal convulsions also occurred. At this time the right temporal decompression site was tense and bulging. Now there was bilateral papilledema with hemorrhages in the right fundus. A left homonymous hemianopia was evident. Nystagmus on lateral and forward gaze was still present. There was some impairment of touch and pain perception in the left hand. A pneumoencephalogram was repeated and revealed considerable dilation of the ventricles of both sides; the third ventricle was now in normal position. The temporal horn on the right was markedly distended and extended outside the bony defect into the soft tissue bulge. Right and left cerebral angiograms revealed distortion of the anterior and middle cerebral arteries which suggested hydrocephalus.

During the first month of this last admission the patient repeatedly developed headache, lethargy, nausea, and occasionally vomited. The severity of these symptoms fluctuated and seemed to correspond to the degree of tension and bulging of the decompression site. Moreover, he improved each time lumbar puncture was performed, fluid withdrawn, and the intracranial pressure lowered.

The patient was considered for re-exploration

TABLE 1
SPINAL TAPS PERFORMED DURING LAST ADMISSION

Date	*Initial Pressure*	*cc. Removed*	*Final Pressure*	*Protein*
10/4	430	3		192
10/30	480	3		350
11/4	520	5		220
11/9 0 hr.	320	30	90	
1 hr.	295			
11/15 0 hr.	420	70	90	
1 hr.	210	30	90	
1½ hr.	110	50	50	
11/16 0 hr.	320	60	90	
1½ hr.	120	15	80	
2½ hr.	150	30	80	
		20	30	
11/17	240	45	30	
11/19	440	90	30	
11/21	110	35	30	
11/22	140	45	30	
11/23	120	25	25	
11/24	100	20	30	
11/25	200	30	30	
11/27	300	70	40	
11/29	305	80	70	
11/30	280	70	40	
12/2	70	15	40	
12/4	355	55	65	435
12/6 more than	600	30	220	390
12/7 " "	600	100	60	240
12/8 " "	600	120	100	244
12/9 " "	600	120	60	250
12/10 " "	600	95	30	350
12/11 " "	600	135	40	
" "	600	40	200	
12/12	320	?	70	
12/13	550	100	30	
	480	60	45	
12/14	600	95	35	
12/16 " "	600	60	40	
" "	600	100	40	
	360	50	60	
12/18 " "	600	100	40	
	420	90	40	
	420	85	30	
12/20	450	105	35	
12/21	500	75	40	
	430	105	60	400

because of the long-term progression of symptoms, the seizures, and the constant electroencephalographic and cerebrospinal fluid abnormalities. It was felt that surgery might elucidate the nature of the calcification and amputation of the right anterior temporal lobe could be performed. However, the patient improved clinically with lowering of the cerebrospinal fluid pressure by lumbar puncture. Further, the dilation of the right temporal horn, as visualized in the pneumoencephalograms (figure 2) and the arteriograms, seemed to obviate the probability of a space-occupying lesion in that area and added further weight to the diagnosis of "serous meningitis." Further investigation to test for impairment of cerebrospinal fluid absorption seemed indicated at this time, and conservative treatment was continued.

Accordingly, phenolsulfonphthalein was injected intrathecally and was found to be excreted in the urine at the rate of 30 per cent in six hours (over five hours longer than normal[7]). The test was repeated during a period when the cerebrospinal fluid pressure was low and absorption was still found to be markedly

decreased. Intravenous phenolsulfonphthalein excretion was tested as a control and revealed normal renal function. These tests and the serial spinal taps done on November 15 and 16 (table 1) showed a rapid reaccumulation of cerebrospinal fluid which probably resulted from faulty reabsorption mechanisms.

After this, the elevated intracranial pressure was treated for the next month by almost daily lumbar punctures (table 1), with rapid withdrawal of large amounts of cerebrospinal fluid. During this time the patient felt better subjectively and improved clinically. His papilledema receded and the decompression site softened after each tap.

After a month, however, this method of treatment suddenly failed. The cerebrospinal fluid pressure suddenly rose to over 600 mm. and could not be brought down to normal levels despite two or three taps a day (table 1). His condition deteriorated progressively. A subarachnoid-peritoneal anastomosis was performed to relieve increased intracranial tension.

Postoperatively the decompression site remained soft, but the patient did not respond well. Two weeks after the operation he suddenly developed repeated episodes of pulmonary edema. No cause was demonstrated and it was suggested that this complication was neurogenic in origin. Despite treatment he declined gradually and progressively and expired after several days.

PATHOLOGIC FINDINGS

Autopsy was limited to examination of the brain. There was a herniation of the tissues of the right frontotemporoparietal area through the operative defect, in which area the gyri were markedly flattened. There was no definite uncal or cingulate herniation. The leptomeninges revealed numerous focal nodules and diffuse areas of opacity (figure 3), apparently due to the presence of a firm white tissue in the subarachnoid space. This was most marked over the ventral aspect of the right temporal lobe and the dorsal aspect of the cerebellum, but such zones of leptomeningeal opacity were present over the entire surface of the brain. The basal cisterns were not involved to any greater degree than other portions of the subarachnoid space. The tissues of the medial aspect of both temporal lobes were softened.

Section of the cerebrum revealed the leptomeningeal nodules to be generally hard and white, with small, softer, hemorrhagic and necrotic zones. The largest such mass was that on the inferior surface of the right temporal lobe where it formed a plaque measuring ap-

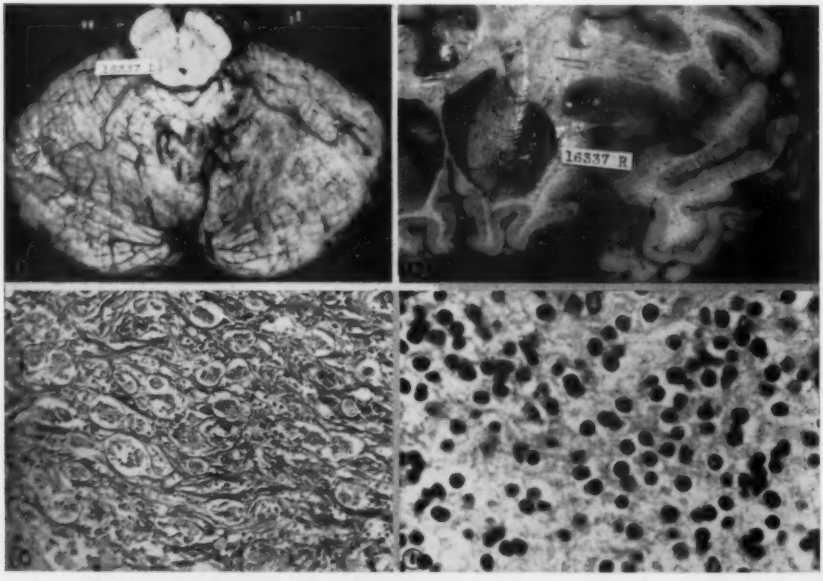

FIG. 3. Dorsal surface of cerebellum showing leptomeningeal opacity.
FIG. 4. Coronal section, right cerebrum, showing extracerebral tumor mass infiltrating the cerebrum.
FIG. 5. Photomicrograph of leptomeninges showing islands of tumor cells embedded in dense fibrous connective tissue. Azocarmine stain.
FIG. 6. Photomicrograph of neoplastic cells within parenchyma, characteristic of the oligodendroglioma. Hematoxylin and eosin stain.

proximately 5 cm. in diameter and 0.8 mm. in thickness (figure 4). Its position correlated well with the calcification seen on the roentgenogram. This mass was in the subarachnoid space for the most part, but in some areas seemed to infiltrate the neural parenchyma. A discrete parenchymal mass was not present. The subjacent neural tissues were markedly compressed, softened, edematous, and presented numerous petechial and larger areas of hemorrhage. The herniated brain tissue was similar in appearance. The lateral ventricles were dilated asymmetrically, that on the left being the larger. The midline structures lay 2 cm. to the left of the midline. The third and fourth ventricles and the aqueduct appeared normal, as did the cerebellum. The caudal end of the medulla formed a mass projecting caudad and lying dorsal to the cephalic portion of the cord. This projection measured approximately 13 mm. in width and 6 mm. in height.

Microscopic sections of the leptomeningeal tumor masses revealed neoplastic cells, isolated and in small clusters, embedded in a densely collagenous connective tissue (figure 5). The cells were uniform in appearance in some areas, and in such sites possessed small dark nuclei, often with the characteristic clear pale perinuclear zone (figure 6). In these areas, glial fibers were demonstrated by the phosphotungstic acid-hematoxylin method. In other areas the cells were larger, darker, and more irregular, and this was particularly noted in zones in which there was a marked fibrosis. At a number of sites, neoplastic cells could be seen infiltrating into the substance of the cortex, either along the perforating vessels or over broader areas. Numerous zones of calcification were present in the areas of parenchymal involvement. The tumor cells were found to infiltrate the leptomeninges diffusely through the entire subarachnoid space. This infiltration was greatest over the area of herniation where the tissue was dense and fibrotic and filled with tumor cells.

The neoplasm was interpreted as being an oligodendroglioma with moderate anaplastic changes and with massive, diffuse infiltration of the subarachnoid space. The medullary malformation was considered to be of the Arnold-Chiari type.

DISCUSSION

The clinical picture at the time of the patient's first hospitalization suggested the possibility of a temporal lobe neoplasm. However, the combination of increased intracranial pressure, relatively normal cerebrospinal fluid protein, normal-sized undistorted ventricles as demonstrated by ventriculography, and the operative findings of only a markedly increased quantity of cerebrospinal fluid led to an initial diagnosis of so-called "serous meningitis." This erroneous impression was strengthened later by the demonstration of defective cerebrospinal fluid absorption and the marked correlation between lowering the intracranial pressure by repeated spinal taps and temporary clinical improvement. Further, it was thought that the repeated absence of cells in the cerebrospinal fluid and the long clinical course made the possibility of a meningeal neoplastic process somewhat remote. Also, it was felt that the dilation of the right temporal horn and the shift of the ventricular system to the right in the later pneumoencephalograms ruled out a right temporal lobe neoplasm.

In retrospect, it can be seen that, whereas these assumptions would ordinarily be valid clinically, they were fallacious in the situation where the pathology was that of a slow-growing neoplasm, diffusely spreading through the subarachnoid space, and producing a marked fibrotic response from the leptomeningeal mesenchymal cells. This fibrotic response impaired the cerebrospinal fluid absorptive mechanisms. The increased intracranial pressure could not be attributed in any significant measure to the bulk of neoplastic cells, since the total quantity of tumor tissue was not great and formed no large discrete mass. Thus, a glioma caused a clinical picture simulating that of "serous meningitis." Possibly a meningeal biopsy at the time of surgery would have been of diagnostic value.

Although the last pneumoencephalogram showed a shift of the ventricular system to the right, postmortem examination demonstrated that the midline structures were shifted to the left. The shift to the right, together with dilation of the right lateral ventricle, was undoubtedly the result of periods of increased intracranial pressure and subsequent herniation of the cerebrum through the operative defect on that side. The subarachnoid-peritoneal anastomosis, which was done later, established free drainage of spinal fluid and resulted in a relatively constant, lowered intracranial pressure. Presumably this eliminated the distorting effect of high intracranial pressure of pushing the cerebrum toward the area of bony defect on the right and allowing the brain to fall back to a midline position. However, it is not clear why still further shift occurred so that midline structures

were found displaced to the left at autopsy.

In three of the four cases described by Beck and Russell,[4] the picture was remarkably similar to that of the patient reported here. These patients had small or undetected primary neoplasms, high cerebrospinal fluid pressure, increased protein, and dilated ventricles. There were no cells in the spinal fluid despite massive invasion of the subarachnoid space. These findings were present before surgery and probably represented increased intracranial pressure caused by blockage of the reabsorbing mechanism of the cerebrospinal fluid. These findings may be characteristic of advanced oligodendrogliomatosis.

The early age at onset of the tumor in this case is not typical. The episodes occurring at the age of two cannot be proved to be an effect of the tumor. Those which occurred at seven years of age were undoubtedly related to the neoplasm. Oligodendrogliomas occurring before the age of ten are rare,[8,9] but of the four cases of oligodendrogliomatosis reported by Beck and Russell, two were children less than seven years of age.

The exact origin of the tumor was not clearly demonstrable. The temporal lobe lesion was the one which was the largest and showed the earliest signs clinically and was probably near the original site. It has been suggested that gliomatous tumors which permeate the subarachnoid space, as occurred in this case, may arise within the substance of a heterotopic glial nest,[5] a a fairly frequent malformation in which central nervous tissue is found within the subarachnoid space.

Of interest is the fact that repeated lumbar punctures were performed without complication in the presence of papilledema. There has long been a general impression that when papilledema and increased intracranial pressure are present, lumbar puncture is a dangerous procedure because of the possibility of causing herniation of the brainstem. As is evident from table 1, repeated lumbar punctures and the rapid withdrawal of large quantities of cerebrospinal fluid under markedly increased pressure had no pernicious effect.

The medullary malformation of the Arnold-Chiari type was probably a purely incidental finding. Although differences of opinion exist, the developmental character of this deformity is attested by many observers. In this and other cases, it is difficult to see how the medullary deformity could have resulted from increased intracranial tension, especially without inducing the much more common herniation of the cerebellar tonsil.[10]

SUMMARY

An unusual case of diffuse oligodendrogliomatosis is described. The clinical picture was marked by a long progressive course and the absence of the usual criteria indicating the presence of a mass. In certain phases the clinical picture simulated "serous meningitis." Despite the presence of papilledema and markedly increased intracranial pressure, numerous lumbar punctures were done. The pathology disclosed at autopsy is described and the mechanism of the increased intracranial pressure in this case is discussed.

Appreciation is expressed to Dr. Morris B. Bender for his interest and helpful criticism.

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CASE REPORT

Chronic Spinal Epidural Hematoma in a Child

G. M. Maxwell, M.D., M.R.C.P. and F. Puletti, M.D.

CHRONIC EPIDURAL HEMATOMA, or chronic hematorrhachis, is an unusual cause of spinal cord compression. An early report was that of Jackson[1] in 1869 who demonstrated an extensive extradural hematoma in a 14 year old girl. Sadka,[2] in his review of the literature, found only 12 cases. Generally rare, the condition is extremely uncommon in children. We have found only one other patient in the pediatric age group, that of Shenkin and Grant.[3] The following report illustrates the lesion and demonstrates some unusual features.

CASE SUMMARY

In May 1955 a four year old boy fell three feet from a hayrick. He sustained a fracture of his left tibia, which was immobilized in a cast for six weeks. After its removal, the parents noted a peculiarity of gait which they attributed to the fracture. In late October 1955 he complained of pain in the chest, apparently of a spasmodic nature and not severe. This disappeared in 24 hours. One week later the pain recurred, similar in site and nature, but accompanied by some neck stiffness. He was seen by a local physician who suspected poliomyelitis. Examination in the local hospital revealed some equivocal neck stiffness and low fever. He improved for 36 hours, then suddenly developed complete paralysis of the lower limbs. Spinal fluid at this time was under pressure, normal in cell content, but high in protein (136 mg. per cent). He was transferred to this unit, having been paralyzed for eight days. When examined the boy was alert, afebrile, and quite cooperative. Cranial nerve function was normal and papilledema absent. He had good motor function in his arms and trunk. The legs were paraplegic and markedly spastic. Spontaneous ankle clonus was seen. The plantar reflexes were extensor and the tendon reflexes grossly exaggerated. The right lower abdominal and cremasteric reflexes were absent. The boy appeared to be enuretic, true overflow incontinence being absent. Sensory examination was unsatisfactory because of the patient's youth, but gross pain appreciation (pin-prick) appeared to be unimpaired.

The provisional clinical diagnosis was that of a compressive cord lesion in the thoracic region. Spinal fluid pressure was 220 mm. of water, there was no pleocytosis, and the protein was 162 mg. per cent. Plain roentgenograms of the spine were normal. An oil myelogram (figure 1) revealed a filling defect from the upper border of the second thoracic vertebra to the midportion of the fourth.

Operation. The thoracic vertebrae were approached by a suitable incision and the spinous processes of the first three removed. The dura thus revealed did not pulsate, and a cyst 2 cm. in diameter was seen over T_2 and T_3. This mass was firmly attached to the dura in the midline and on the left side. A vein crossed the lower portion of the cyst. A small volume (3 cc.) of chocolate-colored fluid was aspirated. Biopsy confirmed that the cyst was hemorrhagic in origin. Therefore, the tangential vein already mentioned was secured and the mass completely removed; on opening the dura, the cord was obviously compressed and pale. Two spinal veins could be seen coursing over the posterior columns; these apparently disappeared at the level of the hematoma, but could be seen again

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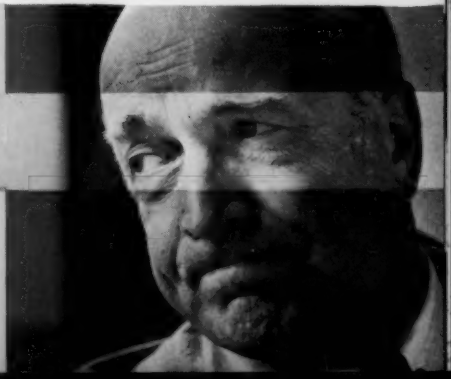

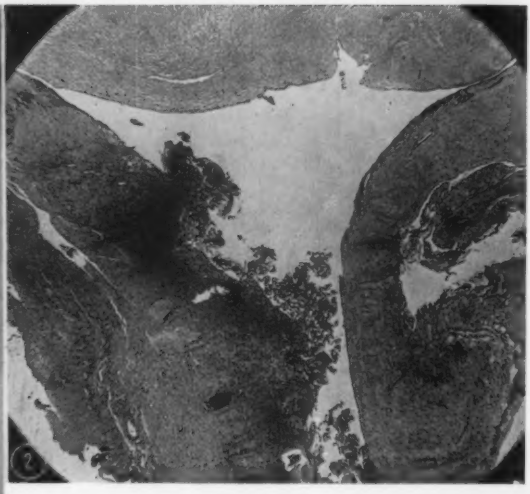

FIG. 1. Oil myelogram demonstrating the filling defect. It extends from the second to the fourth thoracic vertebrae.
FIG. 2. Photomicrograph showing the thickened wall of the epidural vein and an organizing thrombus.

in the segment below it. The dura was left open and the wound closed in the usual fashion.

Pathology (Specimen obtained from hematoma). Microscopic section (figure 2) showed that the mass consisted of a partially organized clot; a rather tortuous and dilated vessel had a focus of hemorrhagic necrosis in its wall. This suggested that the hematoma had its origin from the vein described in the operative findings.

Progress. The laminectomy wound healed readily, but the loss of function and neurologic signs were unchanged for several weeks. Extensive re-education was begun and after two months the boy could walk in parallel bars; his gait, however, was greatly impaired by persistent extensor movement of the legs which was elicited when his feet touched the ground. He was discharged when able to walk with help. Sphincteric control was normal.

Progress was slow but steady, and by August 1956 he could walk and run without help, although he favored his left leg. The reflexes were still exaggerated and the limbs slightly spastic. Bladder and rectal functions were normal.

DISCUSSION

This appears to be another case of chronic epidural hematoma causing paraplegia in

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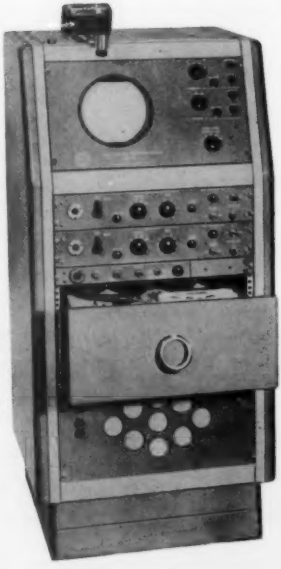

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childhood. Fracture of the vertebrae, in itself insufficient to cause spinal cord compression, has been found associated with chronic extravasation of blood into the epidural space.[4] Minor effort, such as vomiting or urinating, has preceded the onset of symptoms in some reports.[5,6] Sadka's second case, however, had its onset while the patient was sitting quietly in a chair. Hemophilia was recorded as a contributory factor by Priest.[7]

Since the posterior epidural space is the larger,[8] this is the usual site of a hematoma. Our case followed this rule, and this possibly accounts for greater impairment of the pyramidal tracts than of the spinothalamic tracts.

In most instances, paraplegia begins within a short time of the preliminary root pain, although a two-week interval was recorded by Svien, Adson, and Dodge.[9] The symptoms occurred several months after an inury in our patient, and paraplegia occurred more than a week after the onset of what was probably root-pain. Both of these features are unusual in this rare condition. It is conceivable that a minor injury occurred in the epidural vein at the time of the original inujry and that the small, slow-growing cyst delayed symptoms for several months; a single vein was clearly the cause, as demonstrated in figure 2.

The high spinal fluid pressure and increased protein content are quite typical of this condition,[2] and, as in other compressive lesions, the oil myelogram was of great value.

It has been said[9] that prognosis for function is good if early surgery is done. Sadka is more cautious and noted that the hemorrhage may be too extensive for adequate surgery. In the present case, the anemic appearance of the cord was held to imply a bad prognosis; however, good recovery ultimately occurred. It should be mentioned that laminectomy in Sadka's first case revealed a normal pulsating cord; in spite of this, no recovery occurred in his patient. Clearly, prognosis on the basis of macroscopic assessment is not possible.

SUMMARY

A case of chronic epidural hematoma with spinal cord compression is reported in a child. The origin of the lesion was clearly demonstrated and is illustrated. Surgical treatment removing the mass ultimately gave a good functional recovery.

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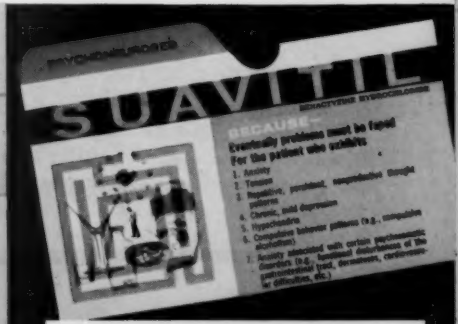
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NEWSLETTER

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AUGUST 1957

Joint Session and Vascular Studies Feature ANA Program A joint session with the American Association of Neuropathologists and papers on vascular disease of the nervous system highlighted the scientific program of the American Neurological Association at its 82nd annual meeting held at the Hotel Claridge in Atlantic City (June 17-19). The joint session presented a symposium on the encephalomyelopathies of infancy and childhood (under the chairmanship of Ben W. Lichtenstein) and studies on the pathology of cerebral vascular anomalies. Other vascular studies included internal carotid thrombosis in children (Davidson, et al.), arterial blood vessel patterns of the brain (Gillilan), anticoagulant therapy (Levy, et al.), anatomic studies of the circle of Willis (Alpers, et al.), and hypothermia (Pool, et al.). Other carefully selected presentations on a wide range of topics rounded out the scientific sessions of 38 papers and four scientific exhibits.... On the social side, President and Mrs. H. Houston Merritt gave a cocktail reception on the Claridge Terrace, Monday evening (June 17). The annual banquet was held Tuesday and was spirited by clever satirical entertainment provided by members of the house staff of the New York Neurological Institute. Included in the performance were lampoons of certain "characters" in neurology, among whom was one frequently seen in the company of a French poodle.

Merritt Speaks of Epilepsy and Progress in Neurology In his opening presidential address at the ANA meeting, H. Houston Merritt described the professional background of his personal interest in epilepsy, reviewed modern concepts of mechanisms underlying seizures, and traced the progress of medical seizure therapy from the middle of the 19th century, when Locock reported good results from bromides, to the introduction of phenobarbital by Hauptmann (1912) and the discovery, in 1937, of the anticonvulsant action of diphenyl hydantoin by Putnam and Merritt. While medical control of seizures is still unsatisfactory, Merritt concluded that the outlook is promising in view of our increasing knowledge of the metabolic defect in epileptogenic foci and of methods for modifying cortical activity.... Dr. Merritt ended his address by pointing to the strides made in neurology during the last decade. Important factors in the march of progress were the

establishment of the National Institute of Neurological Diseases and Blindness, the organization of the American Academy of Neurology, and the support of neurology by many voluntary health agencies each dedicated to a specific neurologic disease. Prospects for the future of neurology in research and training are bright, but more young neurologists should be guided to a proper role in clinical practice, Dr. Merritt believes.

Wechsler Becomes ANA President Israel S. Wechsler is the incoming president, taking office at the end of the 82nd annual meeting of the ANA. Other officers elected are B. J. Alpers, president-elect; R. N. DeJong, first vice-president; and B. S. Ray, second vice-president; Charles Rupp continues as secretary-treasurer and editor of the transactions, with William F. Caveness serving as assistant secretary.... Elected to the council for five years was the retiring president H. Houston Merritt and M. B. Bender for two years.... Newly elected to active membership were D. de R. Daly, C. M. Fisher, D. W. Mulder, Fred Plum, R. P. Schmidt, J. F. Sullivan, Maurice Victor, and D. K. Ziegler; to associate membership: Mary A. B. Brazier, L. T. Kurland, and R. B. Livingston.... The hotel registration of members and guests at this meeting was 474.... The 83rd annual meeting of the ANA will be held again at the Claridge Hotel, Atlantic City, June 16-18, 1958.

Myelin Symposium Precedes ANA Sessions Under the sponsorship of the National Institute of Neurological Diseases and Blindness, a two-day symposium on myelin was held at the Hotel Claridge, Atlantic City (June 15-16), prior to the ANA meeting. These sessions, which were chaired by Saul R. Korey and Donald B. Tower, comprised presentations and discussions from multidisciplinary points of view: Ultrastructure, F. O. Schmidt, Keith Porter, Sarah Luse, J. F. Hartmann, and S. L. Palay; development (genetics), P. J. Harman, Salome Waelsch, and Paul Weiss; chemical development, J. Folch-Pi, Eli Robins, and O. H. Lowry; biology (physiology), Ichiji Tasaki, T. H. Bullock, and A. M. Shanes; tissue culture, Walther Hild, Margaret R. Murray, and A. S. Rose; glial cell, K. A. C. Elliott and Roger Rossiter; chemistry, Heinrich Waelsch, E. P. Kennedy, R. O. Brady, N. S. Radin, Maurice Rapport, and Jonathan Wittenberg; demyelinating diseases, Robert Terry, R. M. Condie, and H. M. Zimmerman. The respective chairmen of the sessions on ultrastructure, development, biology, chemistry, and demyelinating diseases were Edward Dempsey, Alfred Pope, Harry Grundfest, J. Folch-Pi, and Abner Wolf.... Though there was some controversy between the morphologists and neurophysiologists, there appeared to be a growing recognition of the myelin sheath as part of the living cell rather than as a lifeless, extracellular covering.

Houston Neurological Society to Hold Conference on Parkinsonism

William S. Fields, professor and chairman of the division of neurology at Baylor University College of Medicine, reports that, as part of its sixth annual scientific sessions (March 16, 1958), the Houston Neurological Society will hold a symposium on the pathogenesis and treatment of parkinsonism. Among the participants named are Malcolm B. Carpenter, Harry Kaplan, Arthur Ward, Robert Schwab, Russell Meyers, Paul Bucy, Irving Cooper, and A. Earl Walker.

Neurology Training Program Inaugurated at Albert Einstein

Saul R. Korey, professor of medicine (neurology), announces the inauguration of a three-year residency training program in neurology at the Albert Einstein College of Medicine of Yeshiva University. Sixty beds on two wards in the Bronx Municipal Hospital Center have been assigned to neurology, with clinical research laboratories in close proximity. The staff of the neurology program, which is supported by a training grant from the National Institute of Neurological Diseases and Blindness, currently includes three full-time physicians, Saul R. Korey, Labe C. Scheinberg, and Robert Katzman. Another full-time teacher is expected shortly. Supplementing training in clinical neurology, there is an opportunity for residents in neurology to engage in research in the neurologic sciences through an extensive fellowship program on an intradisciplinary basis, which is supported by the National Institute of Mental Health.... The Albert Einstein College of Medicine is about to start its third academic year, having opened in September 1955.

Other AAN Committees and Chairmen Named

Besides the committees and their chairmen announced in the June 1957 issue of the NEWSLETTER, President Forster has appointed the following committee chairmen: Walter O. Klingman, junior prize essay; Howard D. Fabing, reports of officers; Pearce Bailey, membership and policy; and A. B. Baker, general reference.... To handle the possibility of publishing a special meeting number of NEUROLOGY to accommodate the growing number of papers presented at AAN annual meetings, President Forster appointed a special editorial board to assist R. N. DeJong, NEUROLOGY's editor-in-chief. On this special board are, J. L. O'Leary, Chairman; Sidney Carter, A. S. Rose, A. L. Sahs, Joe R. Brown, D. B. Tower, W. F. Windle, and Gilbert Glaser.

Tower Elected Section President

Donald B. Tower was elected president of the AAN Section on Neurochemistry at its initial session at the AAN annual meeting in Boston (April 22-27). Thirty-two papers were presented during the sessions, centering particularly on energetics, lipid metabolism,

and neurohumoral mechanisms. Other section members elected to office were Maynard Cohen, secretary; R. O. Brady, chairman of program committee, and W. K. Jordan, chairman of committee on training in neurology.... Plans for the establishment of other AAN sections in neuroanatomic sciences and neuropharmacology are now in the making.

Briefs The topic for the 1957 meeting of the Association for Research in Nervous and Mental Disease (Hotel Roosevelt, New York City, December 13-14) is, "The Effect of Pharmacologic Agents on the Nervous System." President of the ARNMD is Francis J. Braceland; vice-presidents are Paul H. Hoch and Carl C. Pfeiffer, and secretary-treasurer is Rollo J. Masselink.... On May 20, 1957, at the University of Illinois College of Medicine, a panel discussion was held on tranquilizing drugs (program supported by an educational grant from Wallace Laboratories). Among the panelists were: F. J. Gerty, R. R. Grinker, F. A. Gibbs, R. W. Gerard, J. G. Miller, and D. G. Marquis.... A symposium on the innervation of muscle was held at Utrecht before an invited audience (July 17-20). Participating were representatives from Belgium, Denmark, France, Australia, Czechoslovakia, Germany, England, and Sweden. Present from the U. S. was D. Nachmansohn.... New aspects of health problems will be presented at a one-week course on "Medical Aspects of Workmen's Compensation," (Oct. 21-25) offered by the New York University Post Graduate Medical School (Department of Industrial Medicine) and the American Academy of Compensation Medicine. Inquiries should be addressed to the Office of the Associate Dean, New York University Post Graduate Medical School, 550 First Avenue, New York 16, N. Y..... The Second National Congress of Reeducative Physiotherapy and Functional Recuperation is scheduled to take place in Barcelona, Spain (September 12-14). Further information may be obtained from the Secretario del Congreso, Dr. Jose M.a Poal, Travesera de Gracia, 22, Barcelona.

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References (1) Millichap, J. G., and Hadra, R.: Neurology 6:843, 1956. (2) Settel, E.: Am. Pract. & Digest Treat. 8:443, 1957.

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